TOXICOLOGICAL PROFILE FOR TIN AND COMPOUNDS

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

September 1992

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about tin and its compounds and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Tin has been found in at least 11 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for tin. As EPA evaluates more sites, the number of sites at which tin is found may change. This information is important for you to know because tin may cause harmful health effects and because these sites are potential or actual sources of human exposure to tin.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as tin, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS TIN?

Tin is a soft, white, silvery metal that is insoluble in water. Tin metal is used to make cans for food, beverages, and aerosols. It is present in brass, bronze, pewter, and some soldering materials.

Tin is a metal which can combine with other chemicals to form compounds. When tin is combined with chemicals such as chlorine, sulfur, or oxygen, it is called an inorganic tin compound. Inorganic tin compounds are found in small amounts in the earth's crust. They are present in toothpaste, perfumes, soaps, coloring agents, and dyes.

Tin can also combine with carbon-containing materials to form organotin compounds. These compounds are used in making plastics, food packages, plastic pipes, pesticides, paints, wood preservatives, and rodent (rats and mice) repellants.

There can be tin metal, as well as inorganic and organic tin compounds in the air, water, and soil near places where they are naturally present in the rocks, mined, manufactured, or used. The time each tin compound stays in air, water, or soil differs from compound to compound.

Further information on the properties and uses of tin and its compounds and how they behave in the environment is found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO TIN?

Tin is present in the air, water, soil, and landfills and is a normal part of many plants and animals that live on land and in the water. Tin is also found in the tissues of your body. We do not clearly understand how it gets there, how long it stays, or whether it is needed for your good health and nutrition.

Tin is found naturally in food in amounts of 0.1-l parts per million (ppm). You can be exposed to tin when you eat food or drink juice or other liquids from tin containers. Canned food from lacquered cans contains less than 25 ppm of tin since the lacquer prevents the food from reacting with the tin. Food from unlacquered cans contains up to 100 ppm of tin since the reaction of the food with the can causes some of the tin to dissolve in the contents of the can. Although the tin content of canned food is usually low, the amount can be increased when the food is stored in open cans for a long time. You can also be exposed to higher-than-normal levels of tin when you work in a factory that makes or uses tin. Because tin compounds have many uses, you can be exposed by breathing in tin dusts or fumes or getting tin compounds on your skin. Tin compounds can also be spilled accidentally. If you live near a hazardous waste site, you could be exposed by breathing dusts, touching materials, or drinking water containing tin.

Humans are usually exposed to far less than 1 ppm tin in the air and in water. The amounts in air and water near hazardous waste sites could be more. Young children sometimes eat soil during play. Most soil contains about 0.89 ppm tin. Some soils may contain as much as 200 ppm tin.

Additional information on how you can be exposed to tin compounds is given in Chapter 5.

1.3 HOW CAN TIN ENTER AND LEAVE MY BODY?

Tin can enter your body when you eat contaminated food or drink contaminated water, when you touch or eat soil that has tin in it, or when you breathe tin-containing fumes or dusts. Exposure to contaminated air, water, and soil are ways tin compounds can enter your body near hazardous waste sites. When you eat tin in your food, very little leaves the gastrointestinal tract and gets into your bloodstream. Most tin travels through the intestines and leaves your body in the feces. Some leaves your body in the urine. If you breathe air containing tin dust or fumes, some of the tin could be trapped in your lungs, but this does not affect your breathing if it is a small amount. If you swallow some metallic tin particles, they will leave your body in the feces. Very little tin can enter the body through unbroken skin. Your body can get rid of most inorganic tin in weeks, but some can stay in your body for 2-3 months. Inorganic tin compounds leave your body very quickly, most are gone within a day. Very small amounts of tin stay in some tissues of your body, like the bones, for longer periods of time.

Further information on how tin enters and leaves your body is given in Chapter 2.

1.4 HOW CAN TIN AFFECT MY HEALTH?

Because the inorganic tin compounds usually enter and leave your body rapidly when you breathe them or eat them, they do not usually cause harmful effects. However, human and animal studies show that large amounts of these tin compounds can cause stomach aches, anemia, liver and kidney problems, and skin and eye irritation. Individual organic tin compounds can cause problems with your breathing. They can interfere with the way your brain and nervous system work. Some of these compounds weaken your body's ability to protect you from disease. Inorganic tin compounds do not affect reproductive functions, produce birth defects or cause genetic changes. Inorganic tin compounds do not cause cancer. We do not know at this time if organic tin compounds found in pesticides, plastics, and paints can cause cancer. One organic tin compound used as a pesticide has been called a possible cancer causing substance by the EPA because of pituitary tumors found in female rats during one study.

More information on the health effects of tin in humans and animals is found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TIN?

Because you always have some tin in your body, tests on your urine and feces can be done to tell you something about how much tin is in your body, but not when or how it got there. Such tests, therefore, have limited value as methods of monitoring tin exposure, although they can be useful when exposure concentration are well above the background levels of tin from food and other environmental media.

Further information on how tin can be measured in exposed humans is presented in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Several government agencies and the Congress have acted to protect human health by regulating tin compounds. The EPA has limited the use of certain organotin compounds in paints. The Occupational Safety and Health Administration (0.9%) has established workplace exposure limits of 0.1 milligrams per cubic meter of air (mg/m^3) for organotin compounds, and 0.2 mg/m^3 for tin and inorganic tin compounds. The Food and Drug Administration (FDA) regulates the use of some organic tin compounds in coatings and plastic food packaging.
Additional information on governmental regulations and guidelines regarding tin and compounds is found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of inorganic tin and organotin compounds and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for inorganic tin and organotin compounds based on toxicological studies and epidemiological investigations.

Because there is such a large number of inorganic tin and organotin compounds, only representative compounds have been selected for the discussion of health effects. The selection of compounds has been based on the appropriateness of the data for a given route of administration as well as the specific health effects and toxicological end points being considered. Likewise, human or animal studies have been selected to illustrate specific health effects. However, additional references, review articles, and government reports are provided as applicable in order to assist the reader in understanding more fully the toxicology of the tin compounds.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed- adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

2.2.1 Inhalation Exposure

Little information has been published regarding the effects of inhaled inorganic tin or organotin compounds on human health. Reports of human occupational exposures often involve multiple chemicals and lack details on actual exposure concentrations and conditions. Some reports of humans must also be regarded as anecdotal. The older animal literature (from the 1950s) includes inhalation studies that are lacking in the description of methods and in the reporting of experimental findings. However, it is still possible to characterize some aspects of tin toxicity due to inhalation of inorganic tin and organotin compounds. Exposure levels of the inhaled organotin compounds are expressed as milligrams per cubic meter (mg/m^3) of the specific tin compound unless otherwise noted. Doses are not expressed as doses of tin due to the covanent bond between the tin and the organic moiety. There are no data for specific inorganic tin compounds. Calculations of parts per million (ppm)values are included as appropriate. Table 2-l and Figure 2-l summarize available quantitative information on health effects that have been observed in animals after inhalation exposure to various organotin compounds. Exposure levels are expressed as ppm in Table 2-l and Figure 2-l as well as in Section 1.4. A table and figure are not presented for inorganic compounds due to limitations of the available studies.

2.2.1.1 Death

Inorganic Tin Compounds. No studies were located regarding lethality in humans or animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. Deaths have been reported in humans following exposure to organotins. One worker of 6 died 12 days following exposure to a mixture of half dimethyltin and half trimethyltin chloride vapor that occurred during the cleaning of a caldron at a chemical plant. Maximum exposure was a total of 1.5 hours over a 3-day working period (Rey et al. 1984). No estimates of exposure levels were given. The symptoms preceding death included excretion of high levels of tin in the urine, respiratory depression, and coma. More uncertain is the report of a female worker who died following a drenching with triphenyltin chloride, diphenyltin dichloride, and other unidentified compounds. No estimates of exposure levels were given. Death was apparently caused by renal failure 12 days after exposure (NIOSH 1976). No other studies were located regarding lethality in humans after inhalation exposure to organotin compounds.

Lethality in mice was observed following single or repeated daily exposures to a butyltin mixture (81.2% tributyltin bromide and 3.7% dibutyltin dibromide) together with other unidentified compounds (15.1%) (Igarashi 1959). The concentration was 5.65 mg tin/m3 (1.16 ppm) as the butyltin mixture for different durations of exposure. The tributyltin bromide concentration was 1.1 ppm and that for dibutyltin bromide was 0.06 ppm. For a 2-day, 8-hour/day exposure, approximately 80%-90% of the exposed mice died. Despite the observation of other signs of toxicity (see Section 2.2.1.2) the exposure of the mice to multiple compounds confound the interpretation of the data.

TABLE 2-1. Levels of Significant Exposure to Organotin Compounds - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Form
ACUTE EXPOSURE								
Death								
1	Mouse	2 d 8hr/d				1.1 (80-100% fatality)	Igarashi 1959	$C_{12}H_{27}BrSn$
Systemic								
2	Mouse	6 d 7hr/d	Cardio	0.42			Igarashi 1959	$C_{12}H_{27}BrSn$
			Hepatic			0.42 (blood congestion)		
			Renal			0.42 (glomerular swelling, tubular epithelial lesions)		
Reproductive								
3	Rat	10 d 5hr/d				0.39 (40% decrease in reproduction)	Iwamoto 1960	$C_{12}H_{27}BrSn$
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat	95 d 6hr/d	Resp		0.3 (lung hyperemia, catarrhal bronchitis)		Gohlke et al. 1969	$C_{12}H_{27}ClSn$
			Hepatic		0.3 (minor fatty degeneration)			
			Derm/Oc		0.3 (inflamed eyes, nostrils)			
5	Rat	80 d	Resp			0.39 (bronchitis, edema)	Iwamoto 1960	$C_{12}H_{27}BrSn$
			Cardio			0.39 (myocardial atrophy)		
			Hepatic			0.39 (atrophy, necrosis)		
			Renal			0.39 (swelling and congestion)		
			Other			0.39 (splenic hyperplasia, thickened sheaths)		

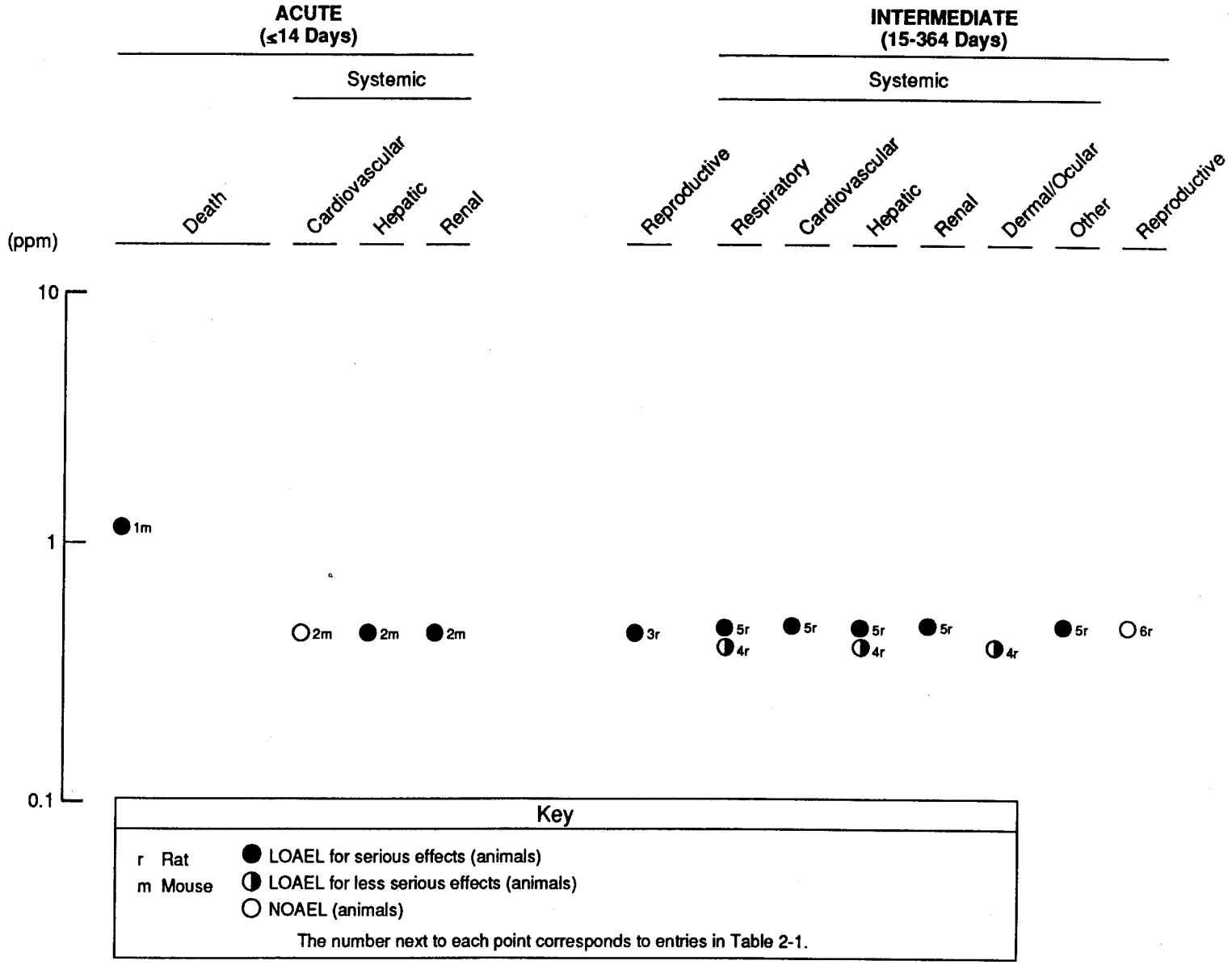
TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Form
Reproductive								
6	Rat	80 d		0.39			Iwamoto 1960	$C_{12}H_{27}BrSn$

[a]The number corresponds to entries in Figure 2-1.

$C_{12}H_{27}FSn$ = tributyltin fluoride; $C_{12}H_{27}ClSn$ = tributyltin chloride; Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory

FIGURE 2-1. Levels of Significant Exposure to Organotin Compounds – Inhalation



Reliable LOAEL values for lethality in rats and mice derived from acute duration studies are recorded in Table 2-l and Figure 2-l.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in humans or animals after inhalation exposure to inorganic tin or organotin compounds.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects.

Inorganic Tin Compounds. Stannic oxide dust or fumes produce a benign form of pneumoconiosis, known as stannosis, in humans (Cutter et al. 1949; Dundon and Hughes 1950; Pendergrass and Pryde 1948). The workers exhibiting this pulmonary condition had industrial exposures ranging from 15 to 20 years. No exposure levels were included in the case reports. In all cases, chest x-rays of the workers showed discrete opaque shadows throughout the lungs, attributed to stannic oxide deposits. However, there was no impairment of pulmonary function or systemic disease. It has also been reported that x-rays of tin foundry workers confirmed more than 150 cases of stannosis by 1959 (Stokinger 1981).

No studies were located regarding respiratory effects in animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. Respiratory depression requiring artificial ventilation occurred in three of six chemical workers. The exposure duration was a total of 1.5 hours over a 3-day working period to a mixture containing half dimethyltin and half trimethyltin chloride (Rey et al. 1984). Although the two surviving workers, who were the most severely affected, developed permanent neurological disabilities, respiratory problems did not persist.

Bis(tributyltin)oxide has been implicated in producing irritation of the upper respiratory tract and chest irritation, tightness, and pain in workers using a rubber material containing bis(tributyltin)oxide. Exposure conditions were not described. No changes were observed in pulmonary function tests (NIOSH 1976).

Inflammatory changes consisting of hyperemia and bronchitis were observed in the respiratory system of rabbits exposed to 4-6 mg/m^3 (0.30-0.45 ppm) tributyltin chloride for 95 days (Gohlke et al. 1969). Histopathology, consisting of severe bronchitis and vascular and alveolar edema, was seen in rats exposed to 2 mg tin/m^3 (0.41 ppm) as a mixture of tributyltin dibromide (0.39 ppm), dibutyltin bromide (0.02 ppm) and

hydrocarbon impurities for 80 days (Iwamoto 1960). Since these were terminal histopathological evaluations only, it is not known whether the changes were reversible or would have produced functional impairment in the animals if exposure had continued.

Hepatic Effects.

Inorganic Tin Compounds. No studies were located regarding hepatic effects in humans and animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. Data concerning hepatic effects of organotins in humans and animals are limited.

Autopsy of the chemical worker who died following exposure to a combination of methyltin salts (see Section 2.2.1.1) revealed massive fatty degeneration of liver cells and necrosis (Rey et al. 1984). This is an important finding since liver toxicity is a constant health effect of exposure to organotin compounds, particularly by the oral route of exposure (see Section 2.2.2.2).

Histological change in the liver of rats, consisting of fatty degeneration, was observed at necropsy of animals killed after a 95-day exposure to 4-6 mg/m^3 (0.30-0.45 ppm) tributyltin chloride (Gohlke et al. 1969). Histopathology, consisting of atrophy and slight necrosis of the liver, was seen in rats exposed to 2 mg tin/m^3 (0.41 ppm) as a mixture of tributyltin dibromide (0.39 ppm), dibutyltin bromide (0.02 ppm) and hydrocarbon impurities for up to 80 days as part of a study of reproductive function (Iwamoto 1960). Atrophy of the liver cells increased with exposure duration in the females. Intermediate sacrifice of the males was not conducted. Some recovery was apparent if exposure to tin was stopped prior to sacrifice. The longer the duration of exposure, the less complete the recovery.

Renal Effects.

Inorganic Tin Compounds. No studies were located regarding renal effects in humans and animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. Data concerning renal effects of organotins in humans and animals are limited.

Autopsy of the one chemical worker who died following exposure to the combination of the methyltin salts (see Section 2.2.1.1) revealed shock kidneys (i.e., proximal tubule degeneration) (Rey et al. 1984). This represents a serious tubule change. The other five exposed men had high tin concentrations in the urine with the highest levels occurring in the most severely affected.

Inhalation exposure of mice to a concentration of 5.65 mg tin/m^3 (1.16 ppm) as a mixture of tributyltin bromide (1.1 ppm), dibutyltin bromide (0.06 ppm) and hydrocarbon impurities for 7 hours per day over 6 days produced pathological changes in the kidney (Igarashi 1959). Necropsy of animals revealed slight degenerative changes in the glomeruli, convoluted tubules, and collecting tubules as well as extramedullary hematopoiesis. More extensive kidney pathology was observed in rats exposed to 2 mg tin/m^3 (0.4 ppm) as tributyltin bromide, and 0.39 dibutyltin bromide) (0.02 ppm) for 2 hours per day for 80 days. Kidney damage consisted of extensive congestion and swelling of the renal tubular epithelium (Iwamoto 1960).

Dermal/Ocular Effects.

Inorganic Tin Compounds. Mild irritation of the skin and mucous membranes is known to be caused by inorganic tin salts (WHO 1980). However, no specific studies were located regarding dermal/ocular effects in humans and animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding dermal/ocular effects in humans after inhalation exposure to organotin compounds. Occupational exposure produces such effects as discussed in Section 2.2.3.1.

Dermal effects were observed during inhalation studies in mice that were exposed to a butyltin mixture (30 parts tributyltin bromide to 1 part dibutyltin bromide) and consisted of reddening of the skin and dilatation of the blood vessels of the nose, feet, and tail (Igarashi 1959). Inflamed eyes and nasal mucous membranes were observed in the last month of a 95-day inhalation study of tributyltin chloride in female rats (Gohlke et al. 1969). Concentrations of 4-6 mg/m^3 (0.30-0.45 ppm) for 6 hours/day, 5 days/week were used. From these acute- and intermediate-duration studies with different compounds, the skin and eye irritation potential of organotins was demonstrated.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to inorganic tin or organotin compounds. However, some lymph node atrophy was observed in rats exposed to a butyltin mixture for 14 days (Iwamoto 1960) (see Section 2.2.1.6).

2.2.1.4 Neurological Effects

Inorganic Tin Compounds. No studies were located regarding neurological effects in humans and animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. One study provides some information on neurobehavioral changes in humans after exposure to organotin compounds (dimethyl and trimethyl tin chloride). Case reports on six chemical workers exposed to the methyltins, describe headache, tinnitus, deafness, impaired

memory, disorientation, aggressiveness, psychotic and other severe neuropsychiatric behavior, syncope, and loss of consciousness as symptoms of exposure. The two surviving workers with the highest urinary tin levels exhibited fixed neurological effects which were not resolved more than 6 years after exposure. The remaining three survivors returned to work but had memory loss which persisted for 6 months (Rey et al. 1984).

No other studies were located regarding neurological effects in humans after inhalation exposure to organotin compounds.

The neurotoxicity of trimethyltin and other organotin compounds has been studied extensively following oral exposure in animals (see Section 2.2.2.4). However, no definitive studies were located regarding neurological effects in animals after inhalation exposure to organotin compounds. It was reported that no histopathological changes were observed in the brains of mice from a 6-day inhalation exposure to 2.12 mg tin/m^3 (0.44 ppm) as a mixture of tributyltin bromide (0.42 ppm) dibutyltin bromide (0.02 ppm) and hydrocarbon impurities (Igarashi 1959).

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to inorganic tin or organotin compounds.

2.2.1.6 Reproductive Effects

Inorganic Tin Compounds. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding reproductive effects in humans after inhalation exposure to organotin compounds.

Rats were exposed to a nominal concentration of 2 mg tin/m^3 (0.41 ppm) as a mixture of tributyltin bromide (81.2%) with other compounds such as dibutyltin dibromide in acute- and intermediate-duration exposures to assess reproductive effects (Iwamoto 1960). This tin exposure was equivalent to 0.39 ppm tributyltin bromide and 0.02 ppm dibutyltin bromide. Pregnancy rates were markedly reduced after 4 weeks to 3 months of exposure; however, at least partial reversibility of the effects was seen when exposure was discontinued. Histopathological evaluations were made in separate studies of different exposure durations (14-80 days) followed by recovery periods. No changes were seen in males but atrophy of the glandular uterus was observed as early as 14 days of exposure in females. Examinations of other tissues revealed systemic lymph node and liver atrophy as early as 14 days of exposure. All effects were reversible during the recovery period. Although a mixture of butyltin compounds was used, the results of this study suggest some impairment of female reproductive functions after inhalation of the compounds.

No other studies were located regarding reproductive effects in animals after inhalation exposure to organotin compounds.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans and animals after inhalation exposure to inorganic tin or organotin compounds. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans and animals after inhalation exposure to inorganic tin or organotin compounds.

2.2.2 Oral Exposure

In contrast to the limited information on the inhalation toxicity of tin compounds (Section 2.2.1), there are more data regarding potential effects of ingested or orally administered organotin compounds, particularly as evaluated and characterized in animal studies. Although there is less information concerning health effects produced by oral exposure to inorganic tin compounds, the data from animal studies do allow some characterization of health effects of these compounds. Dosages are expressed as milligrams of tin per kilogram of body weight per day (mg tin/kg/day) as the specific inorganic tin compound fed or administered orally. Table 2-2 and Figure 2-2 summarize available quantitative information on health effects that have been observed in animals after oral exposure to inorganic tin compounds. Similar information for organotin compounds is given in Table 2-3 and Figure 2-3. Dosages are expressed as mg/kg/day as the specific organotin compound due to the covalent bond between the tin and the organic moiety.

2.2.2.1 Death

Inorganic Tin Compounds. No studies were located regarding lethality in humans after oral ingestion of inorganic tin compounds.

In animals, the lowest oral dose that produced deaths in rats following a single gavage administration was 473 mg/kg body weight stannous chloride (NTP 1982,). However, all rats survived doses up to 945 mg/kg/day when the compound was fed in the diet for 14 days (NTP 1982). For mice, the lowest oral dose producing death following a single gavage administration was 378 mg/kg body weight stannous chloride (NTP 1982). All mice survived the 14-day feeding of the compound up to dietary levels of 2,457 mg/kg/day. These studies were performed in order to set doses for the chronic bioassay of stannous chloride in rats and mice (see Section 2.2.2.8).

TABLE 2-2. Levels of Significant Exposure to Inorganic Tin Compounds - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Sn/kg/day)	LOAEL (effect) Less serious (mg Sn/kg/day)	LOAEL (effect) Serious (mg Sn/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(GW)	1 d 1x/d				473 (1/5 females died on day 3)	NTP 1982	$SnCl_2$
2	Mouse	(GW)	1 d 1x/d				378 (1/5 males and 1/5 females died on day 3)	NTP 1982	$SnCl_2$
Systemic									
3	Mouse	(F)	14 d 7d/wk	Other		1229 (males and females gained less weight than those in the lowest dose group)		NTP 1982	$SnCl_2$
INTERMEDIATE EXPOSURE									
Death									
4	Rat	(F)	13 wk 7d/wk				315 (4/10 males died)	deGroot et al. 1973	$SnCl_2$
Systemic									
5	Rat	(F)	4 wk 7d/wk	Cardio	315			deGroot et al. 1973	$SnCl_2$
				Gastro	95	315 (slightly distended small and large intestines)			
				Hemato	32	95 (decreased hemoglobin and hematocrit)			
				Hepatic	32	95 (bile duct hyperplasia, homogeneous cell cytoplasm)			
				Renal	315				
				Other	32	95 (30% decreased body weight gain and decreased food intake)			
6	Rat	(F)	4 wk 7d/wk	Cardio	390			deGroot et al. 1973	SnS
				Hemato	117	390 (significant increase in hematocrit in males)			
				Hepatic	390				
				Renal	390				
				Other	390				

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Sn/kg/day)	LOAEL (effect) Less serious (mg Sn/kg/day)	LOAEL (effect) Serious (mg Sn/kg/day)	Reference	Form
7	Rat	(F)	4 wk 7d/wk	Cardio	325			deGroot et al. 1973	$Sn_3(PO_4)_2$
				Gastro	98	325 (slightly distended small and large intestine)			
				Hemato	33	98 (decreased hemoglobin and hematocrit)			
				Hepatic	9.8	33 (liver enlargement in females)			
				Renal	325				
				Other	33	98 (30% decreased body weight gain in males)			
8	Rat	(F)	13 wk 7d/wk	Cardio	440			deGroot et al. 1973	SnO
				Hemato	440				
				Hepatic	440				
				Renal	440				
				Other	440				
9	Rat	(F)	4 wk 7d/wk	Gastro		7.9 (increased intestinal length)		Janssen et al. 1985	$SnCl_2$
				Hemato		7.9 (decreased hemoglobin)			
				Other		7.9 (17% lower body weight as compared to controls)			
10	Rat	(F)	13 wk 7d/wk	Cardio	315			deGroot et al. 1973	$SnCl_2$
				Gastro		315 (distended intestines)			
				Hemato	32	95 (decreased hemoglobin and hematocrit)			
				Hepatic	32	95 (decreased alkaline phosphatase, decrease in cytoplasmic organelles)			
				Renal	315				
				Other	32	98 (decreased body weight compared to controls [>10%] and decreased food intake for the first 2 weeks)	315 (decreased body weight as compared to controls [40%] caused termination of level - week 9)		

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Sn/kg/day)	LOAEL (effect) Less serious (mg Sn/kg/day)	LOAEL (effect) Serious (mg Sn/kg/day)	Reference	Form
11	Rat	(F)	4 wk 7d/wk	Cardio	85			deGroot et al. 1973	$Sn(C_{18}H_{33}O_2)_2$
				Hemato	85				
				Hepatic	85				
				Renal	85				
				Other	85				
12	Rat	(F)	4 wk 7d/wk	Cardio	390			deGroot et al. 1973	SnO_2
				Hemato	390				
				Hepatic	390				
				Renal	390				
				Other	390				
13	Rat	(F)	4 wk 7d/wk	Cardio	275			deGroot et al. 1973	$SnSO_4$
				Gastro	275				
				Hemato	28	83 (decreased hemoglobin and hematocrit)			
				Hepatic	83	275 (slightly decreased liver/ body weight ratio, homogenous cell cytoplasm)			
				Renal	275				
				Other	28	83 (16% decreased body weight gain and decreased food intake in males)			
14	Rat	(F)	4 wk 7d/wk	Cardio	220			deGroot et al. 1973	$SnC_4H_4O_6$
				Hemato	22	66 (decreased hemoglobin and hematocrit)			
				Hepatic	66	220 (bile duct hyper-plasia, homo-genous cell cytoplasm)			
				Renal	220				
				Other	22	66 (11% decreased body weight gain in males)			
15	Rat	(F)	13 wk 7d/wk	Gastro	60	120 (gross distention of cecum and reddened gastric mucosa)		NTP 1982	$SnCl_2$
				Cardio	236				
				Hemato	236				
				Hepatic	236				
				Renal	236				
				Other		236 (7.8% lower body weight as compared to controls)			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Sn/kg/day)	LOAEL (effect) Less serious (mg Sn/kg/day)	LOAEL (effect) Serious (mg Sn/kg/day)	Reference	Form
16	Rat	(F)	4 wk 7d/wk	Gastro		28 (change in intestinal morphology)		Janssen et al. 1985	$SnCl_2$
17	Rat	(F)	4 wk 7d/wk	Cardio	285			deGroot et al. 1973	SnC_2O_4
				Hemato	29	86 (decreased hemoglobin and hematocrit)			
				Hepatic	29	86 (bile duct hyperplasia, homogenous cell cytoplasm)			
				Renal	285				
				Other	29	86 (18-25% decreased body weight gain and decreased food intake)			
18	Mouse	(F)	13 wk 7d/wk	Gastro	157	311 (gross distention of the cecum)		NTP 1982	$SnCl_2$
				Cardio	2457				
				Hemato	2457				
				Hepatic	2457				
				Renal	2457				
				Other		157 (11.7% decreased body weight gain in males)			
CHRONIC EXPOSURE									
Death									
19	Rat	(W)	42 mo 7d/wk				0.7 (decreased longevity in females by 11%)	Schroeder et al. 1968	$SnCl_2$
Systemic									
20	Rat	(F)	105 wk 7d/wk	Cardio	63			NTP 1982	$SnCl_2$
				Gastro	63				
				Hepatic	63				
				Renal	63				
				Other	63				
21	Rat	(W)	42 mo 7d/wk	Hepatic		0.7 (fatty degeneration)		Schroeder et al. 1968	$SnCl_2$
				Renal		0.7 (tubular degeneration, vacuolization)			
				Other		0.7 (11-16% decreased body weight as compared to controls)			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Sn/kg/day)	LOAEL (effect) Less serious (mg Sn/kg/day)	LOAEL (effect) Serious (mg Sn/kg/day)	Reference	Form
22	Mouse	(F)	105 wk 7d/wk	Cardio	164			NTP 1982	$SnCl_2$
				Gastro	164				
				Hepatic	164				
				Renal	164				
				Other	164				
23	Mouse	(W)	18 mo 7d/wk	Other	0.7			Schroeder and Balassa 1967	$SnCl_2$

[a]The number corresponds to entries in Figure 2-2.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (GW) = gavage - water; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; SnC_2O_4 = stannous oxalate; $SnC_4H_4O_6$ = stannous tartrate; $Sn(C_{18}H_{33}O_2)_2$ = stannous oleate; $SnCl_2$ = stannous chloride; SnO_2 = stannic oxide; $Sn_2O_3N_2$ = stannous nitrate; $Sn_3(PO_4)_2$ = stannous orthophosphate; SnS_2 = stannous sulfide; $SnSO_4$ = stannous sulfate; (W) = water; wk = week(s)

FIGURE 2-2. Levels of Significant Exposure to Inorganic Tin Compounds – Oral

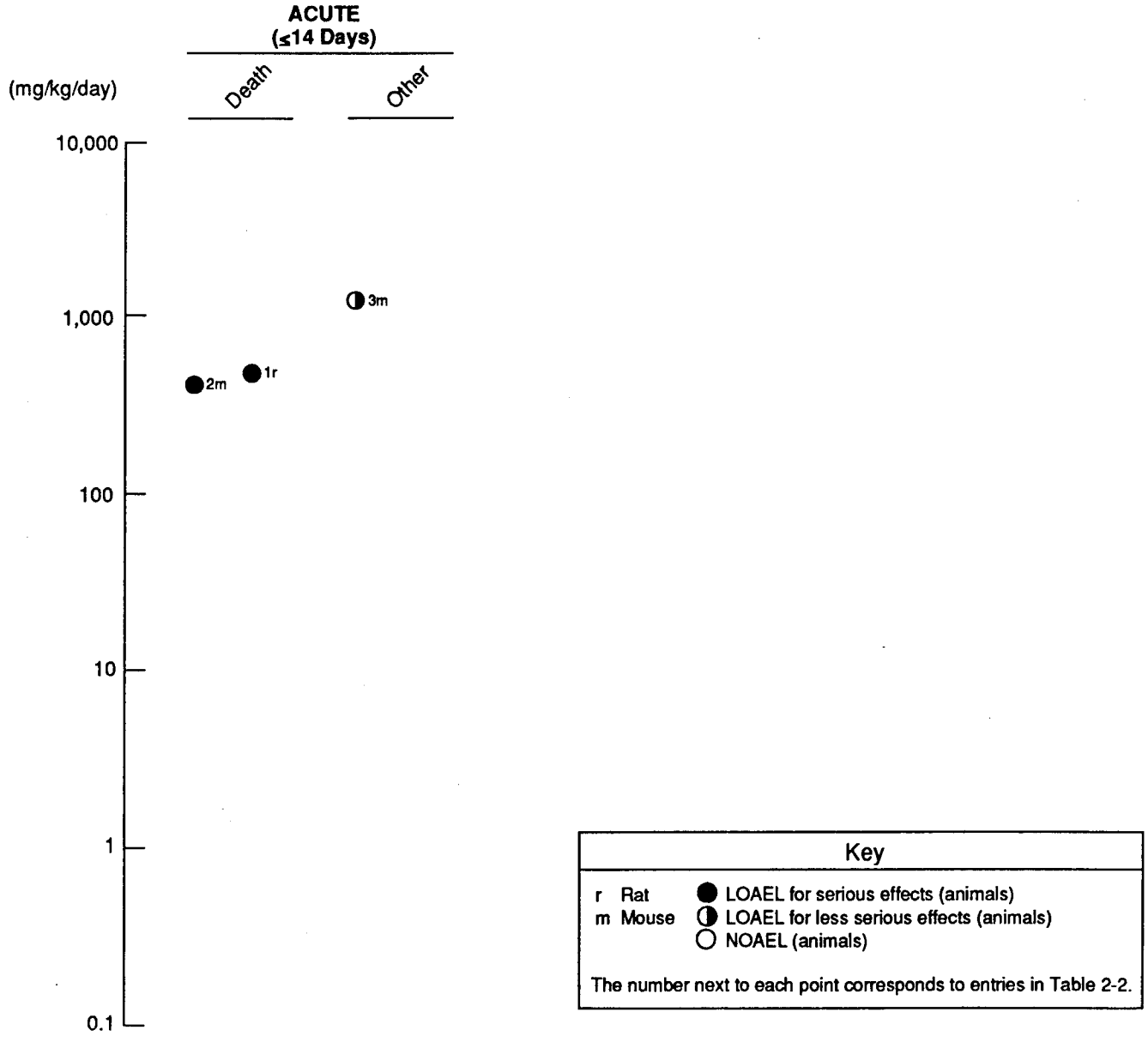


FIGURE 2-2 (Continued)

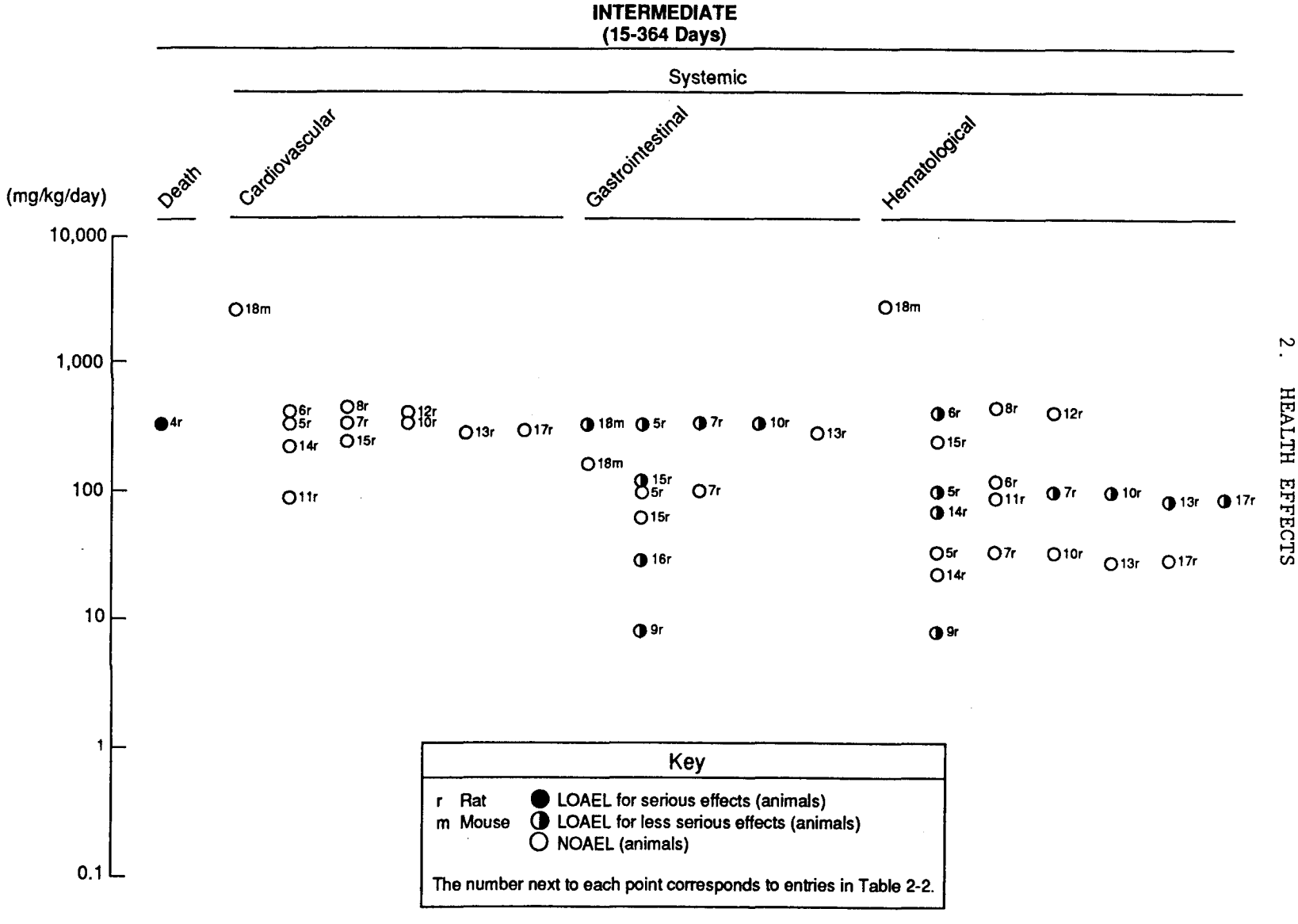


FIGURE 2-2 (Continued)

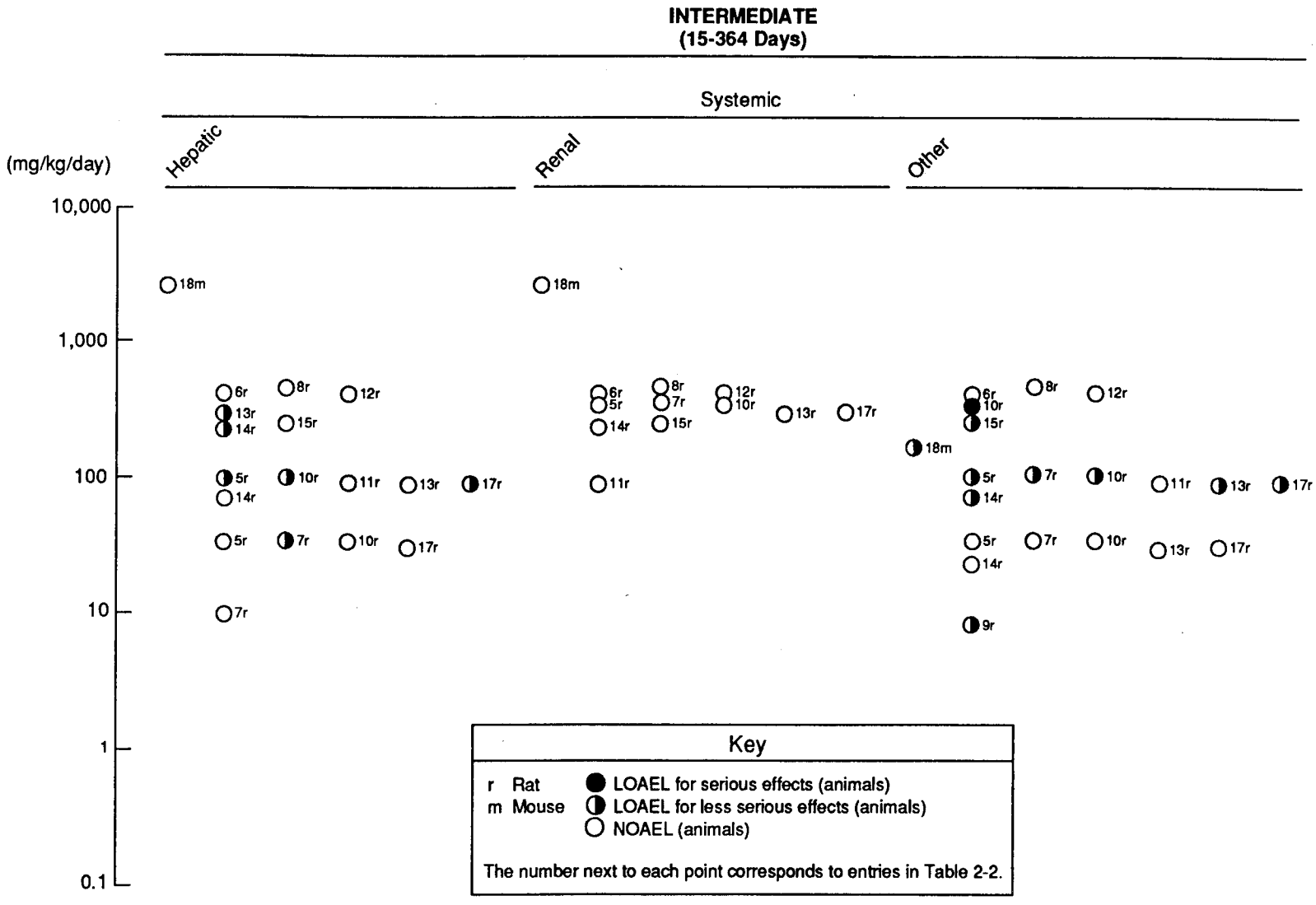


FIGURE 2-2 (Continued)

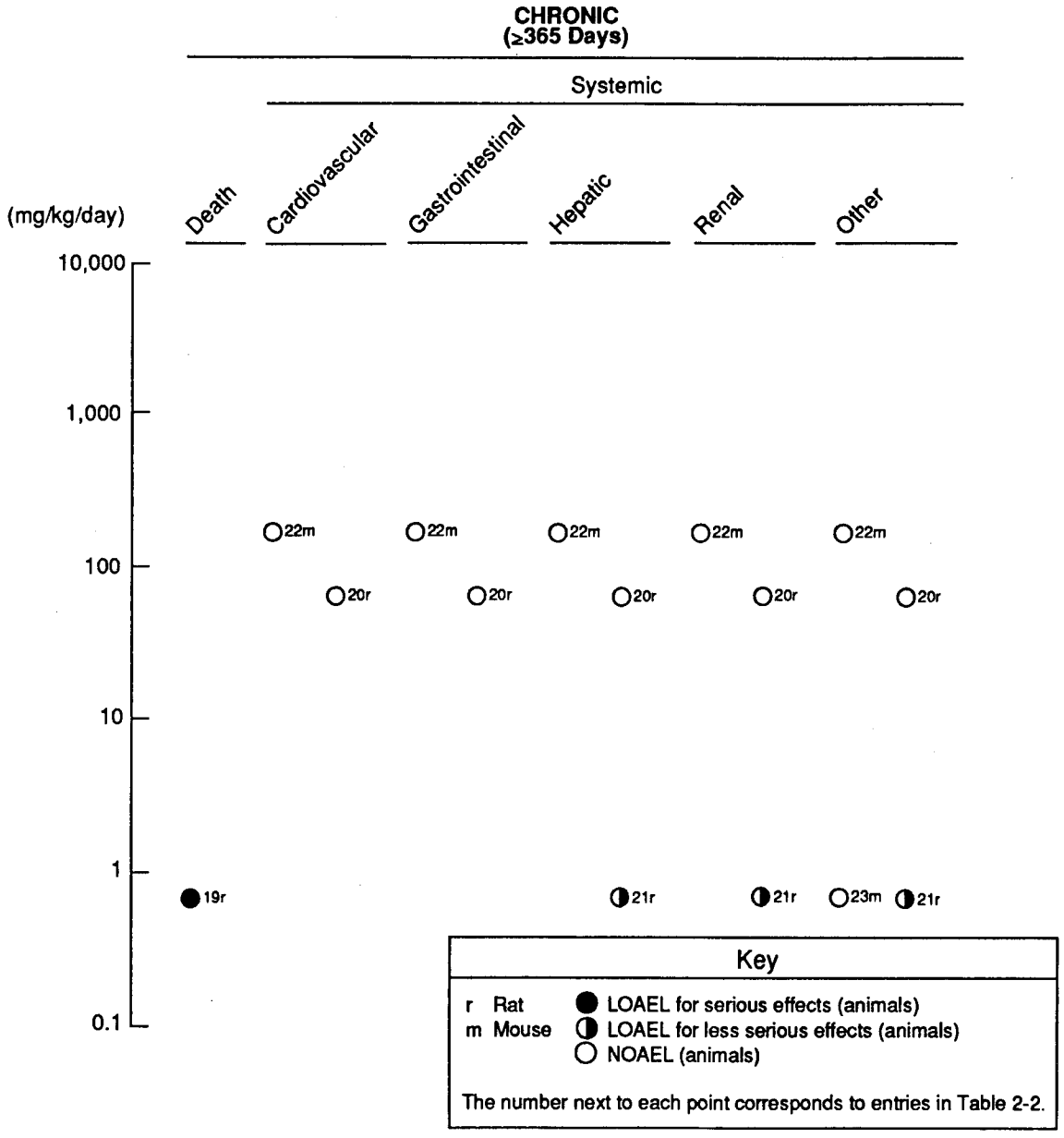


TABLE 2-3. Levels of Significant Exposure to Organotin Compounds - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				148 (LD50)	Elsea and Paynter 1958	$C_{24}H_{54}OSn_2$
2	Rat	(GO)	4 d 1x/d				50 (death of 30%-50%)	Barnes and Magee 1958	$C_8H_{16}Cl_2Sn$
3	Rat	(GO)	1 d 1x/d				14 (LD50)	Aldridge et al. 1987	$C_4H_{11}BrSn$
4	Rat	(GW)	1 d 1x/d				194 (LD50)	Elsea and Paynter 1958	$C_{24}H_{54}OSn_2$
5	Rat	(GO)	1 d 1x/d				12.6 (LD50)	Brown et al. 1979	C_3H_9ClSn
Systemic									
6	Rat	(GO)	1 d 1x/d	Renal		3 (slightly dilated proximal tubules and impaired organ function)	10 (marked proximal tubule necrosis, impaired organ function)	Opacka and Sparrow 1985	C_3H_9ClSn
7	Rat	(GO)	4 d 1x/d	Hepatic			50 (bile duct necrosis)	Barnes and Magee 1958	$C_8H_{16}Cl_2Sn$
				Gastro		50 (distention of stomach)			
8	Mouse	(GO)	1 d 1x/d	Gastro			4000 (hemorrhages in stomach and intestine)	Pelikan and Cerny 1970	$C_4H_9Cl_3Sn$
				Renal			4000 (steatosis of renal cortex and hyperemia of renal medulla)		
				Resp		4000 (impaired respiration)			
9	Mouse	(GO)	1 d 1x/d	Gastro			4000 (hemorrhages in stomach and intestine)	Pelikan and Cerny 1970	$C_{14}H_{28}O_3S_3Sn$
				Renal			4000 (steatosis of renal cortex and hyperemia of renal medulla)		
10	Mouse	(GO)	1 d 1x/d	Gastro			4000 (hemorrhages in stomach and intestine)	Pelikan and Cerny 1970	$C_9H_{10}O_2Sn$
				Renal			4000 (steatosis of renal cortex and hyperemia of renal medulla)		

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
11	Mouse	(GO)	1 d 1x/d	Gastro			4000 (hemorrhages in stomach and intestine)	Pelikan and Cerny 1970	$C_4H_{10}SOSn$
				Renal			4000 (steatosis of renal cortex and hyperemia of renal medulla)		
12	Hamster	(GO)	1 d 1x/d	Hepatic			30 (bile duct necrosis)	Jang et al. 1986	$C_8H_{18}Cl_2Sn$
Immunological									
13	Rat	(F)	2 wk			2.5 (decreased weights of lymphoid organs)		Seinen et al. 1977b	$C_{16}H_{34}Cl_2Sn$
14	Rat	(GO)	10 d 1x/d			1.25 (decrease in thymus weight) 5 (LP responses suppressed)		Smialowicz et al. 1989	$C_{24}H_{54}OSn_2$
15	Rat	(F)	2 wk			2.5 (decreased weights of lymphoid organs)		Seinen et al. 1977b	$C_8H_{18}Cl_2Sn$
Neurological									
16	Rat	(GW)	1 d 1x/d				7.5 (neuronal damage - mainly olfactory cortex, fascia dentata)	Chang et al. 1983	C_3H_9ClSn
17	Rat	(GO)	1 d 1x/d				10 (convulsions)	Brown et al. 1979	C_3H_9ClSn
18	Rat	(GO)	1 d 1x/d				7.5 (edema, necrosis)	Aldridge et al. 1987	$C_5H_{13}ClSn$
19	Rat	(GO)	1 d 1x/d				20 (edema, necrosis)	Aldridge et al. 1987	$C_4H_{11}BrSn$
20	Rat	(G)	1 d 1x/d			5 (altered nerve response to electrical stimulation)		Dyer and Boyes 1984	$C_3H_{10}OSn$
21	Mouse	(GO)	1x				4000 (convulsions, impaired respiration)	Pelikan and Cerny 1970	$C_{30}H_{45}Sn$
22	Mouse	(GO)	1 d 1x/d				4000 (hypoactivity, convulsions)	Pelikan and Cerny 1970	$C_{14}H_{28}O_3S_3Sn$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
23	Mouse	(GO)	1x				4000 (convulsions, impaired respiration)	Pelikan and Cerny 1970	$C_4H_{10}O_2Sn$
24	Mouse	(GO)	1x				4000 (convulsions, impaired respiration)	Pelikan and Cerny 1970	$C_4H_{10}SOSn$
25	Mouse	(GW)	1 d 1x/d				3 (neuronal damage - mainly hippo-campal, fascia dentata)	Chang et al. 1983	C_3H_9ClSn
26	Mouse	(GW)	1 d 1x/d			1 (reduced norepinephrine levels)		Ali et al. 1983	$C_3H_{10}OSn$
27	Hamster	(GO)	1 d 1x/d				3 (neuronal degeneration)	Brown et al. 1984	C_3H_9ClSn
28	Monkey	(GO)	1 d 1x/d				3 (ataxia, neuronal damage)	Brown et al. 1984	C_3H_9ClSn
29	Gerbil	(GO)	1 d 1x/d				3 (neuronal damage)	Brown et al. 1984	C_3H_9ClSn
Developmental									
30	Mouse	(GO)	10 d Gd 6-15 1x/d				1.2 (cleft palate and other bone abnormalities)	Davis et al. 1987	$C_{24}H_{54}OSn_2$
Reproductive									
31	Rabbit	(GW)	1x/d Gd 6-18		.3	0.9 (significant decrease in maternal body weight)		Rodwell 1987	$C_{18}H_{16}OSn$
32	Mouse	(GO)	10 d Gd 6-15 1x/d		11.7	23.4 (decreased maternal weight gain)	35 (decreased number of implantations and living fetuses)	Davis et al. 1987	$C_{24}H_{54}OSn_2$
INTERMEDIATE EXPOSURE									
Death									
33	Rat	(W)	11 wk				1.4 (death)	Smith 1973	$C_{24}H_{54}O_4SSn_2$
Systemic									
34	Rat	(GO)	4 wk 7d/wk	Hemato		4 (binds to hemoglobin)		Brown et al. 1979	C_3H_9ClSn

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
35	Rat	(GO)	15 d 1x/d	Hepatic		17.5 (increased heme oxygenase activity, decreased activity of microsomal enzymes)		Mushtaq et al. 1981	$C_{32}H_{64}O_4Sn$
36	Rat	(F)	6 wk 7d/wk	Other		4 (7% reduced body weight as compared to controls)		Van Loveren et al. 1990	$C_{24}H_{54}OSn_2$
37	Rat	(GO)	26 wk 5x/wk	Other			12 (> 20% decrease in body weight)	Funahashi et al. 1980	$C_{24}H_{54}OSn_2$
38	Rat	(F)	6 wk	Hemato	2.5	7.5 (significant decrease in hemoglobin (males), increased alkaline phosphatase activity)		Seinen and Willems 1976	$C_{16}H_{34}Cl_2Sn$
39	Rat	(F)	3-4 wk	Other	1.25			Vos et al. 1984b	$C_{18}H_{16}OSn$
40	Rat	(W)	3 wk 7d/wk	Musc/skel		4.2 (atrophy of fibers in soleus muscle)		Richman and Bienkamper 1984	$C_6H_{15}BrSn$
41	Rat	(W)	4 wk	Other			0.8 (50% decrease in body weight)	Reiter et al. 1980	$C_6H_{15}BrSn$
42	Rat	(GO)	99d 5x	Other		2.5 (40% reduction in weight gain during 1st week)		Gaines and Kimbrough 1968	$C_{18}H_{16}OSn$
43	Rat	(F)	6 wk 7d/wk	Other		20 (decreased insulin)	80 (decreased thyroxine, thyroid stimulating hormone and insulin, increased leutinizing hormone)	Krajnc et al. 1984	$C_{24}H_{54}OSn_2$
44	Rat	(F)	4 wk 7d/wk	Hemato		5 (decreased mean corpuscular volume, eosinophils)	80 (abnormalities in all hematological components)	Krajnc et al. 1984	$C_{24}H_{54}OSn_2$
				Hepatic	5	20 (increased hepatic enzyme activity)	320 (liver necrosis and bile duct hyperplasia)		
				Other	20	80 (decreased weight gain)			

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
45	Dog	(F)	13 wk	Cardio Hemato Hepatic Renal	0.646 0.646 0.646 0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
46	Dog	(F)	27 wk	Cardio Hemato Hepatic Renal	0.646 0.646 0.646 0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
47	Dog	(F)	4 wk	Cardio Hemato Hepatic Renal	0.646 0.646 0.646 0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
Immunological									
48	Rat	(GO)	26 wk 5x/wk			3 (decreased thymus weight)	6 (severe decrease in thymus weight)	Funahashi et al. 1980	$C_{24}H_{54}OSn_2$
49	Rat	(F)	28 d			2.5 (progressive decrease in thymus weight, decreased cell count and viability)		Seinen and Willems 1975	$C_{16}H_{34}Cl_2Sn$
50	Rat	(GO)	24 d 3x/wk (10 total doses)			10 (decrease in thymus weight, increase in spleen weight, LP responses suppressed, NK responses suppressed)		Smialowicz et al. 1989	$C_{24}H_{54}OSn_2$
51	Rat	(F)	6 wk			2.5 (decreased thymus weight, popliteal lymph node weight)		Seinen and Willems 1976	$C_{16}H_{34}Cl_2Sn$
52	Rat	(F)	4 wk 7d/wk				80 (atrophy of thymus and peripheral lymphoid organs)	Krajnc et al. 1984	$C_{24}H_{54}OSn_2$
53	Rat	(F)	3-4 wk			1.25 (changes in immune response)		Vos et al. 1984b	$C_{18}H_{16}OSn$
54	Rat	(F)	6 wk 7d/wk			1 (reduced natural killer cell activity)		Van Loveren et al. 1990	$C_{24}H_{54}OSn_2$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
55	Rat	(GO)	24 d 3x/wk (10 total doses)			5 (decrease in thymus weight, increase in spleen weight, LP responses suppressed, NK responses suppressed)		Smialowicz et al. 1989	$C_{24}H_{54}OSn_2$
56	Rat	(GO)	24 d 3x/wk (10 total doses)			5 (decrease in thymus weight, LP responses suppressed) 10 (decrease in spleen weight)		Smialowicz et al. 1989	$C_{24}H_{54}OSn_2$
57	Mouse	(F)	4 wk		19.5			Seinen et al. 1977b	$C_8H_{18}Cl_2Sn$
58	Mouse	(F)	4 wk		19.5			Seinen et al. 1977b	$C_{16}H_{34}Cl_2Sn$
59	Dog	(F)	27 wk		0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
60	Dog	(F)	4 wk		0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
61	Dog	(F)	13 wk		0.646			Sachsse et al. 1987	$C_{18}H_{16}OSn$
Neurological									
62	Rat	(W)	11 wk				1.4 (paralysis)	Smith 1973	$C_{24}H_{54}O_4SSn_2$
63	Rat	(GO)	4 wk 7d/wk				4 (neuronal alterations in brain)	Brown et al. 1979	C_3H_9ClSn
64	Rat	(W)	4 wk			0.4 (diminsted maze activity and startle response)	0.8 (paralysis)	Reiter et al. 1980	$C_6H_{15}BrSn$
65	Rat	(W)	3 wk 7d/wk				4.2 (hind limb paralysis followed by by recovery, demyelination in spinal cord and peripheral nerves)	Richman and Bienkamper 1984	$C_6H_{15}BrSn$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
66	Rat	(W)	22 d 7d/wk				2.8 (motor dysfunction, splitting of peripheral myelin sheaths and edema of brain)	Graham and Gonatas 1973	$C_{24}H_{54}O_4SSn_2$
67	Rat	(W)	11 wk				1.9 (paralysis)	Smith et al. 1973	$C_{24}H_{54}O_4SSn_2$
68	Dog	(F)	4 wk		0.646			Sachsse et al. 1987	$C_{19}H_{16}OSn$
69	Dog	(F)	13 wk		0.646			Sachsse et al. 1987	$C_{19}H_{16}OSn$
70	Dog	(F)	27 wk		0.646			Sachsse et al. 1987	$C_{19}H_{16}OSn$
CHRONIC EXPOSURE									
Death									
71	Rat	(F)	78 wk 7d/wk				3.33 (10% decrease in survival)	NCI 1978a	$C_{12}H_{24}O_4Sn$
72	Rat	(F)	78 wk 7d/wk		3.75			NCI 1978b	$C_{19}H_{16}OSn$
73	Rat	(F)	104 wk				0.4 (29/50 rats died prior to the conclusion of the study)	Tennekes et al. 1989b	$C_{19}H_{16}OSn$
74	Mouse	(F)	80 wk				20.16 (25/50 females died before the end of the study)	Tennekes et al. 1989a	$C_{19}H_{16}OSn$
75	Mouse	(F)	78 wk 7d/wk				9.88 (5% decrease in survival)	NCI 1978a	$C_{12}H_{24}O_4Sn$
76	Mouse	(F)	78 wk 7d/wk				4.88 (20% decrease in survival)	NCI 1978b	$C_{19}H_{16}OSn$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
Systemic									
77	Rat	(F)	104 wk	Cardio	6.2			Tennekes et al. 1989b	$C_{18}H_{16}OSn$
				Hemato	5.2				
				Musc/skel		0.3 (atrophy of skeletal muscle)			
				Hepatic		0.4 (portal sclerosis and bile duct proliferation)			
				Renal	6.2				
				Other		0.4 (cystoid lesions and hyperplasia of the pituitary)			
78	Rat	(F)	78 wk 7d/wk	Resp	3.75			NCI 1978b	$C_{18}H_{16}OSn$
				Cardio	3.75				
				Gastro	3.75				
				Hemato	3.75				
				Hepatic	3.75				
				Renal	3.75				
				Derm/oc	3.75				
79	Rat	(F)	78 wk 7d/wk	Resp	6.65			NCI 1978a	$C_{12}H_{24}O_4Sn$
				Cardio	6.65				
				Gastro	6.65				
				Hemato	6.65				
				Musc/skel	6.65				
				Hepatic	6.65				
				Renal	6.65				
80	Rat	(F)	30 mo	Hemato		2.5 (increased platelets)		Wester et al. 1986	$C_{24}H_{54}OSn_2$
				Hepatic		2.5 (reduced glycogen)			
				Renal		2.5 (increase in age-related degenerative lesions)			
81	Rat	(F)	52 wk	Cardio	6.2			Tennekes et al. 1989b	$C_{18}H_{16}OSn$
				Hemato	0.4	1.3 (significant decrease in hemoglobin and hematocrit in females; increased prothrombin time in males)			
				Hepatic	0.4	1.6 (portal sclerosis and bile duct proliferation in females)			
				Renal	6.2				
				Other	0.4	1.3 (cystoid pituitary lesions)			

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
82	Mouse	(F)	78 wk 7d/wk	Resp	9.75			NCI 1978b	$C_{18}H_{16}OSn$
				Cardio	9.75				
				Gastro	9.75				
				Hemato	9.75				
				Hepatic	9.75				
				Renal	9.75				
				Derm/oc	9.75				
83	Mouse	(F)	80 wk	Cardio	20.16			Tennekes et al. 1989a	$C_{18}H_{16}OSn$
				Hemato	20.16				
				Hepatic		15.24 (increased liver to body weight ratio; hyperplastic nodules)			
				Renal	20.16				
				Derm/oc		20.16 (skin lesions, females more sensitive than males)			
				Other		15.24 (reduced body weight gain)			
84	Mouse	(F)	78 wk 7d/wk	Resp	19.76			NCI 1978a	$C_{12}H_{24}O_4Sn$
				Cardio	19.76				
				Gastro	19.76				
				Hemato	19.76				
				Hepatic	19.76				
				Renal	19.76				
85	Dog	(F)	52 wk	Cardio	0.593			Sachsse et al. 1987	$C_{18}H_{16}OSn$
				Hemato	0.593				
				Hepatic	0.593				
				Renal	0.593				
Immunological									
86	Rat	(F)	52 wk			0.3 (reduction in serum immuno-globins IG1, IG2, IG2C, IGA, and increase in IGM)		Tennekes et al. 1989b	$C_{18}H_{16}OSn$
87	Rat	(F)	30 mo			2.5 (increased immunoglobulin levels of IgM and decreased IgG)		Wester et al. 1986	$C_{24}H_{54}OSn_2$
88	Rat	(F)	78 wk 7d/wk		3.75			NCI 1978b	$C_{18}H_{16}OSn$
89	Rat	(F)	104 wk		6.2			Tennekes et al. 1989b	$C_{18}H_{16}OSn$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
90	Mouse	(F)	78 wk 7d/wk		19.76			NCI 1978a	$C_{12}H_{24}O_4Sn$
91	Mouse	(F)	78 wk 7d/wk		9.75			NCI 1978b	$C_{18}H_{16}OSn$
92	Mouse	(F)	80 wk			15.24 (decreased levels of serum immunoglobins)		Tennekes et al. 1989a	$C_{18}H_{16}OSn$
93	Dog	(F)	52 wk		0.593			Sachsse et al. 1987	$C_{18}H_{16}OSn$
Neurological									
94	Rat	(F)	104 wk			0.3 (degenerative neuropathy of sciatic nerve)		Tennekes et al. 1989b	$C_{18}H_{16}OSn$
95	Rat	(F)	78 wk 7d/wk		3.75			NCI 1978b	$C_{18}H_{16}OSn$
96	Rat	(F)	78 wk 7d/wk		6.65			NCI 1978a	$C_{12}H_{24}O_4Sn$
97	Mouse	(F)	78 wk 7d/wk		19.76			NCI 1978a	$C_{12}H_{24}O_4Sn$
98	Mouse	(F)	78 wk 7d/wk		9.75			NCI 1978b	$C_{18}H_{16}OSn$
99	Dog	(F)	52 wk		0.593			Sachsse et al. 1987	$C_{18}H_{16}OSn$
Reproductive									
100	Rat	(F)	78 wk 7d/wk		3.75			NCI 1978b	$C_{18}H_{16}OSn$
101	Rat	(F)	104 wk			0.3 (Leydig cell hypertrophy and tubular atrophy of the testes)		Tennekes et al. 1989b	$C_{18}H_{16}OSn$
102	Mouse	(F)	78 wk 7d/wk		9.75			NCI 1978b	$C_{18}H_{16}OSn$
103	Mouse	(F)	78 wk 7d/wk		19.76			NCI 1978a	$C_{12}H_{24}O_4Sn$

TABLE 2-3 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
Cancer									
104	Rat	(F)	104 wk				1.6 CEL (pituitary tumors)	Tennekes et al. 1989b	$C_{18}H_{16}OSn$
105	Rat	(F)	104 wk				5.2 CEL (testicular tumors)	Tennekes et al. 1989b	$C_{19}H_{16}OSn$
106	Mouse	(F)	80 wk				15.24 CEL (liver tumors)	Tennekes et al. 1989a	$C_{19}H_{16}OSn$

[a]The number corresponds to entries in Figure 2-3.

$C_4H_{10}SOSn$ = butylthiostannoic acid; $C_4H_{10}O_2Sn$ = butylstannoic acid; $C_{12}H_{24}O_4Sn$ = dibutyltin diacetate; $C_8H_{18}Cl_2Sn$ = dibutyltin dichloride; $C_4H_{11}BrSn$ = dimethyltin bromide; $C_4H_9Cl_3Sn$ = mono-n-butyltin trichloride; $C_{14}H_{28}O_3S_3Sn$ = mono-n-butyltin tris(2-ethylhexylmercaptoacetate) C_3H_9ClSn = trimethyltin chloride; $C_5H_{13}ClSn$ = methyldiethyltin chloride; $C_{19}H_{32}O_2Sn$ = tributyltin benzoate; $C_{14}H_{30}O_2Sn$ = tributyltin acetate; $C_{12}H_{27}ClSn$ = tributyltin chloride; $C_{30}H_{45}Sn$ = tributyltin oleate; $C_{16}H_{34}Cl_2Sn$ = dioctyltin dichloride; $C_3H_{10}OSn$ = trimethyltin hydroxide; $C_{24}H_{54}O_4SSn$ = triethyltin sulfate; $C_{18}H_{16}Osn$ = triphenyltin hydroxide; $C_6H_{15}BrSn$ = triethyltin bromide; $C_{10}H_{22}OSn$ = triethyltin acetate; $C_{24}H_{54}OSn_2$ = tributyltin oxide; $C_{32}H_{64}O_4Sn$ = dibutyltin dilaurate; $C_{18}H_{16}OSn$ = triphenyltin hydroxich; $C_{24}H_{54}O_4SSn_2$ = tributyltin sulfate; Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (GO) = gavage - oil; (GW) = gavage - water; Gastro = gastrointestinal; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; LP = lymphoproliferative response; Musc/skel = musculoskeletal; NK = natural killer cell response; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s)

FIGURE 2-3. Levels of Significant Exposure to Organotin Compounds – Oral

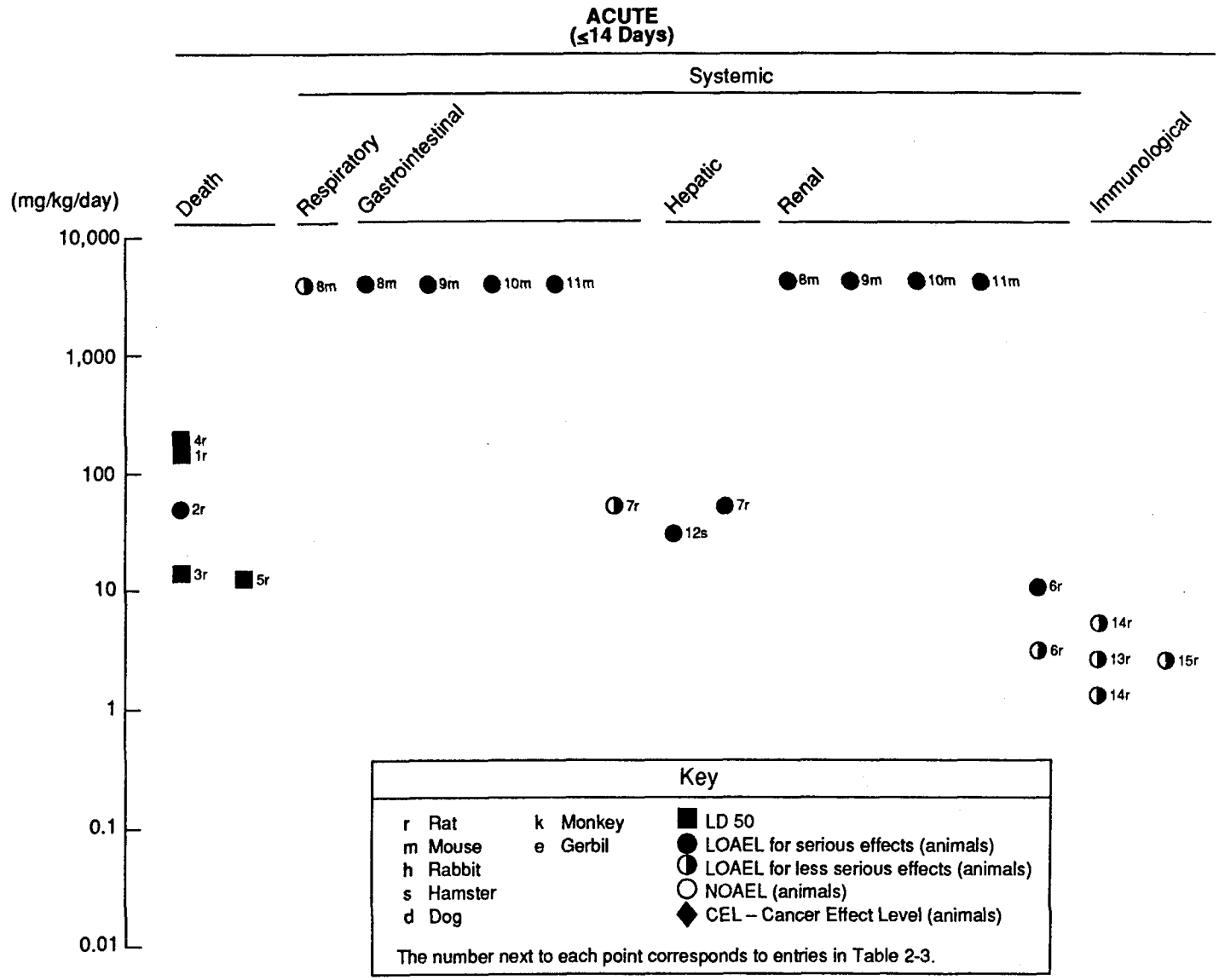


FIGURE 2-3 (Continued)

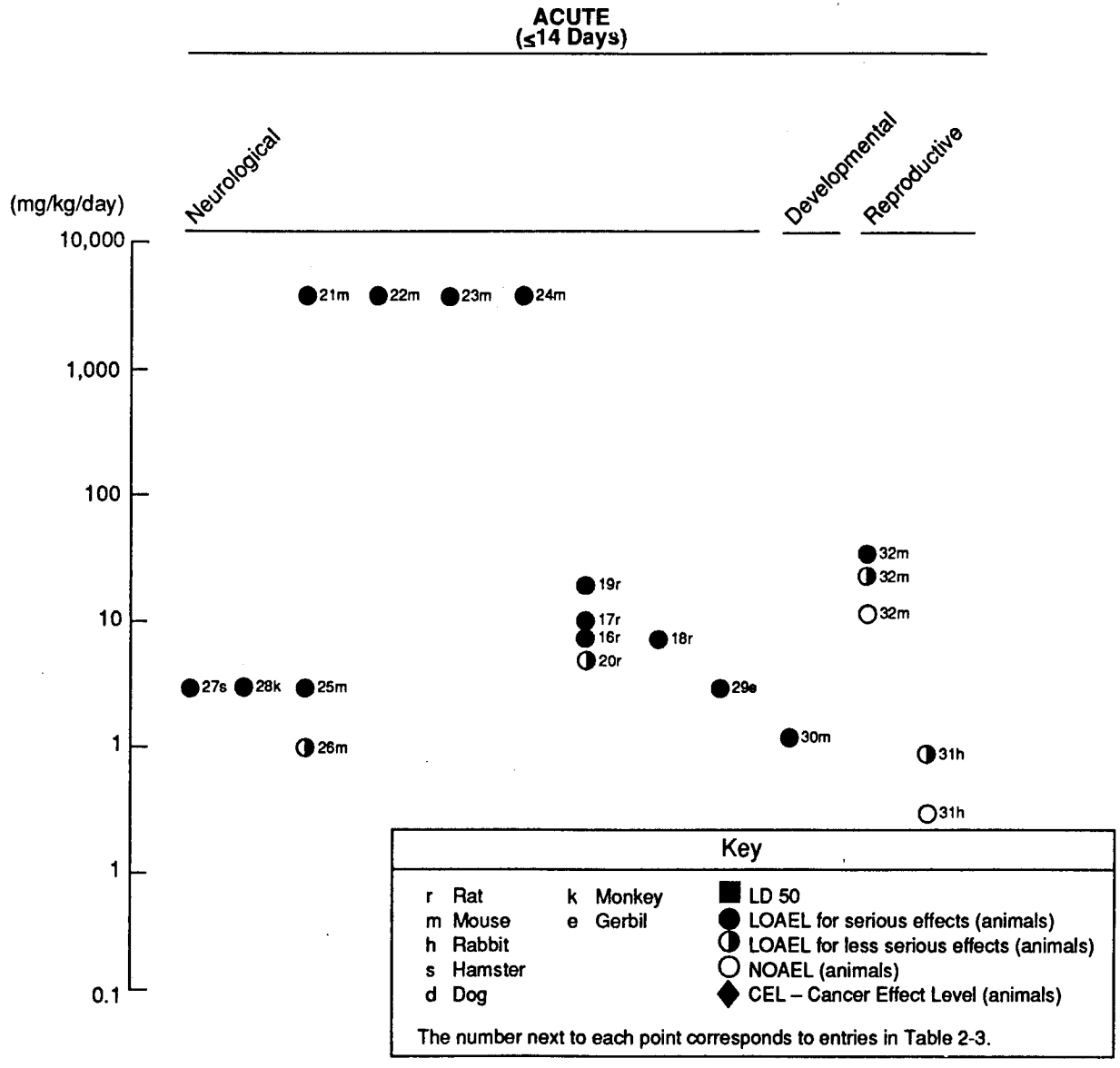


FIGURE 2-3 (Continued)

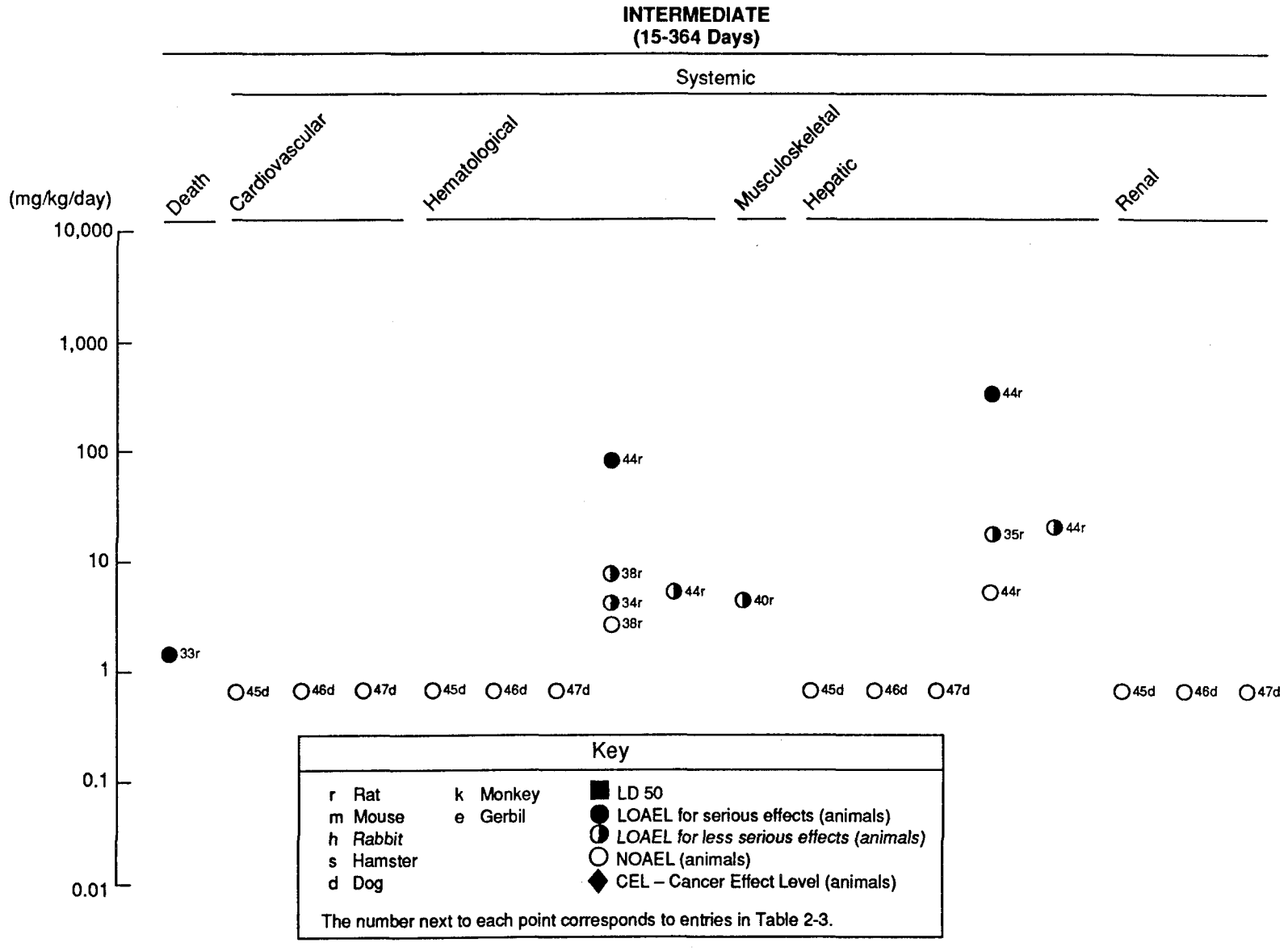


FIGURE 2-3 (Continued)

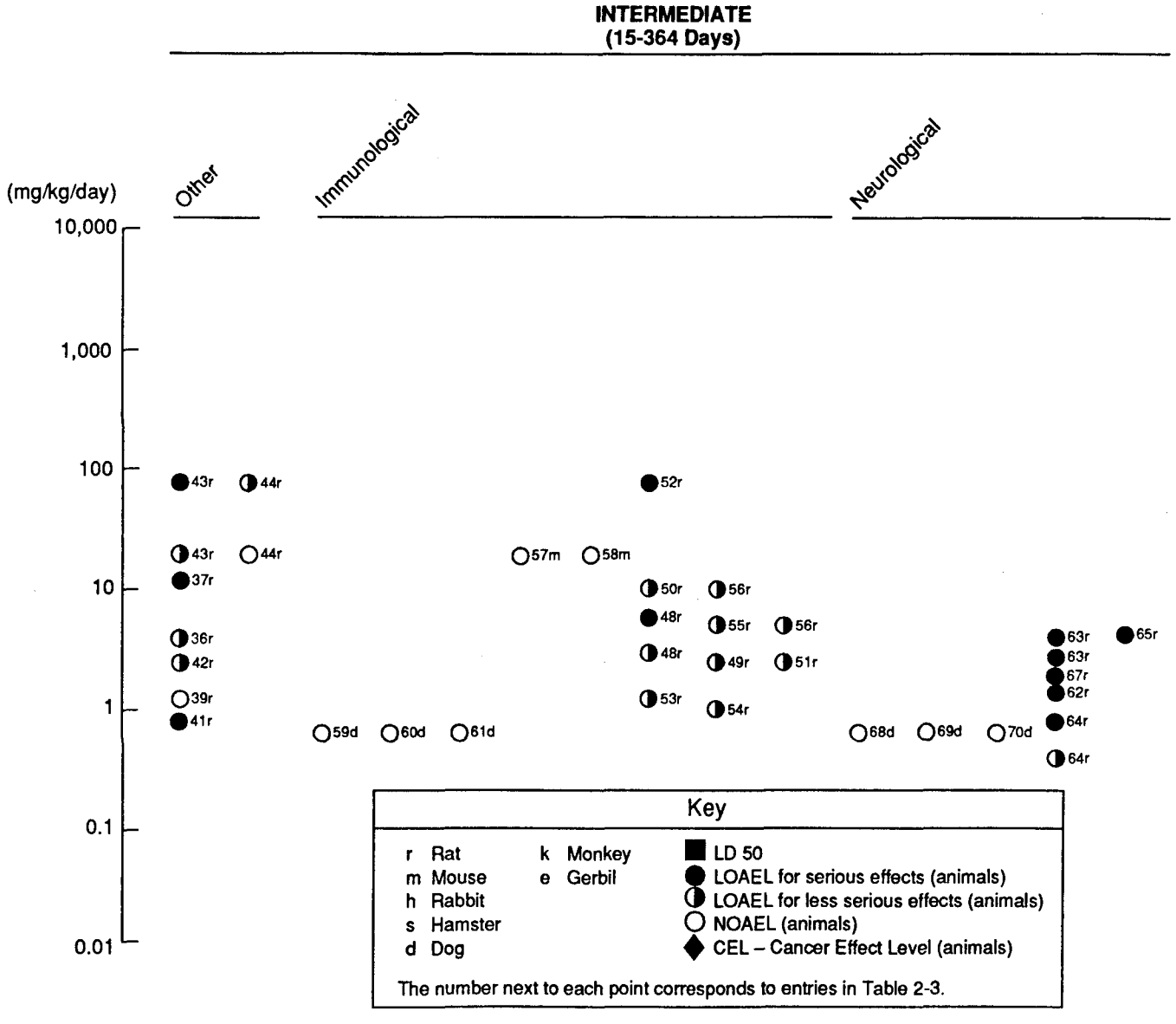


FIGURE 2-3 (Continued)

CHRONIC
(≥365 Days)

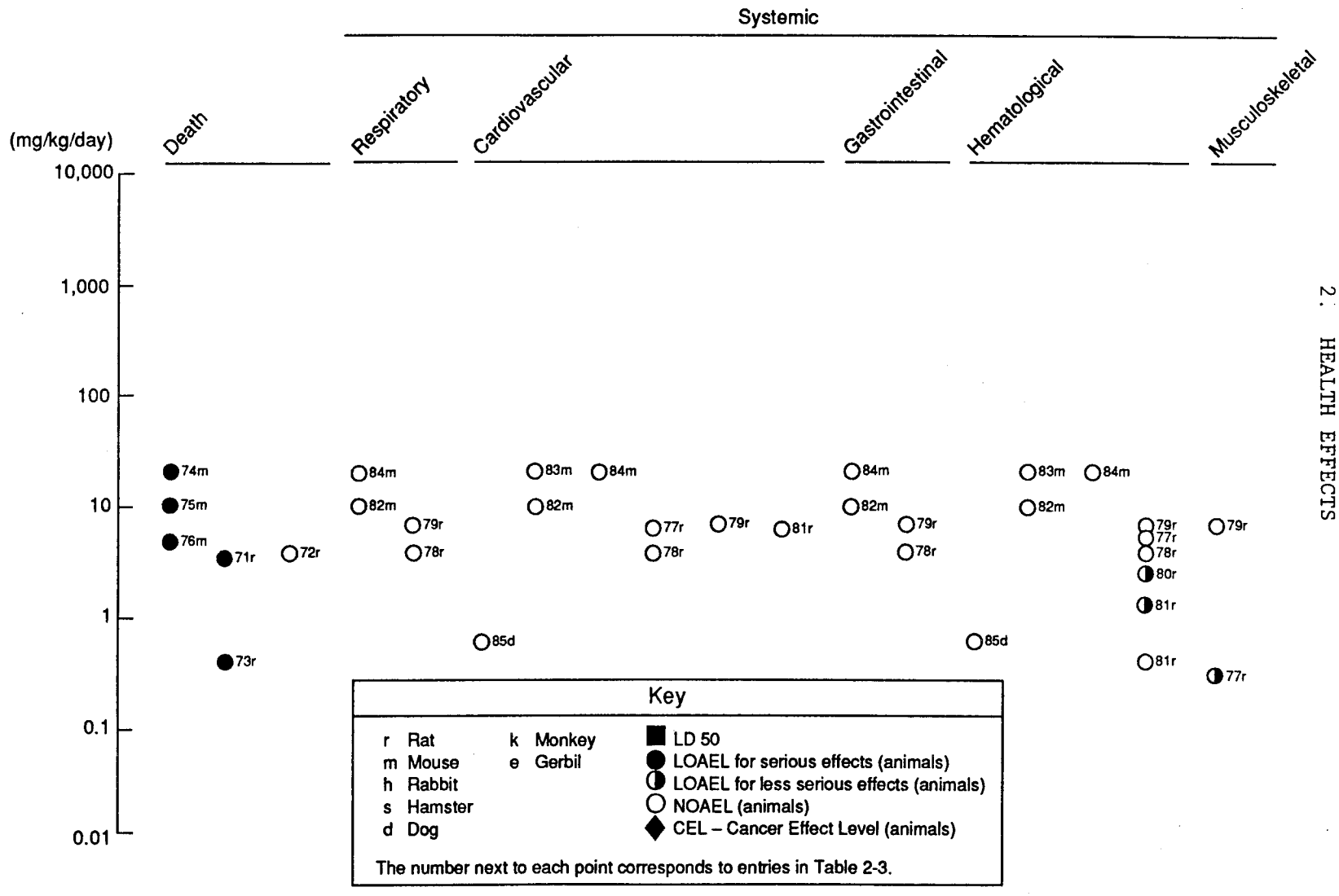


FIGURE 2-3 (Continued)

CHRONIC
(≥365 Days)

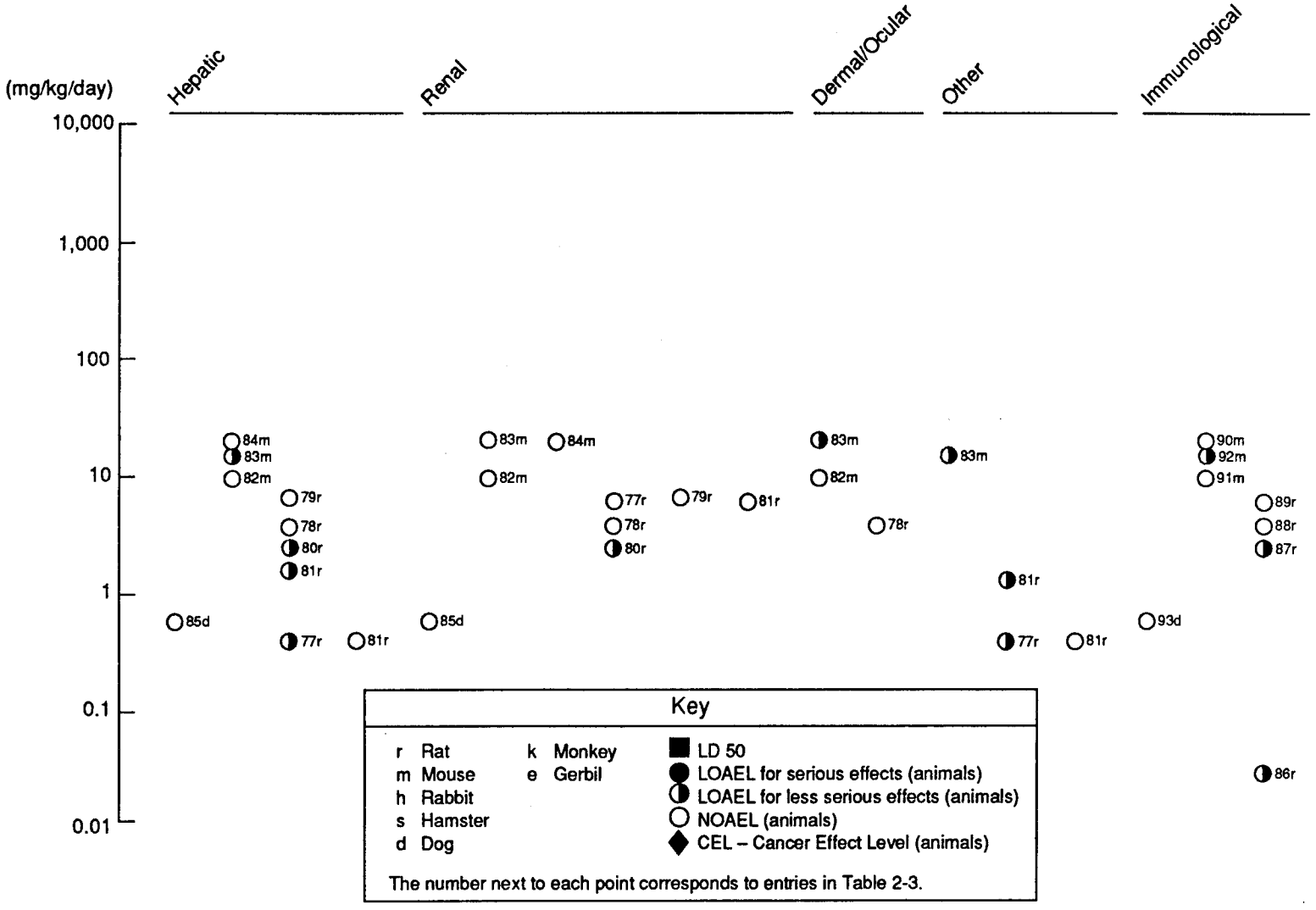
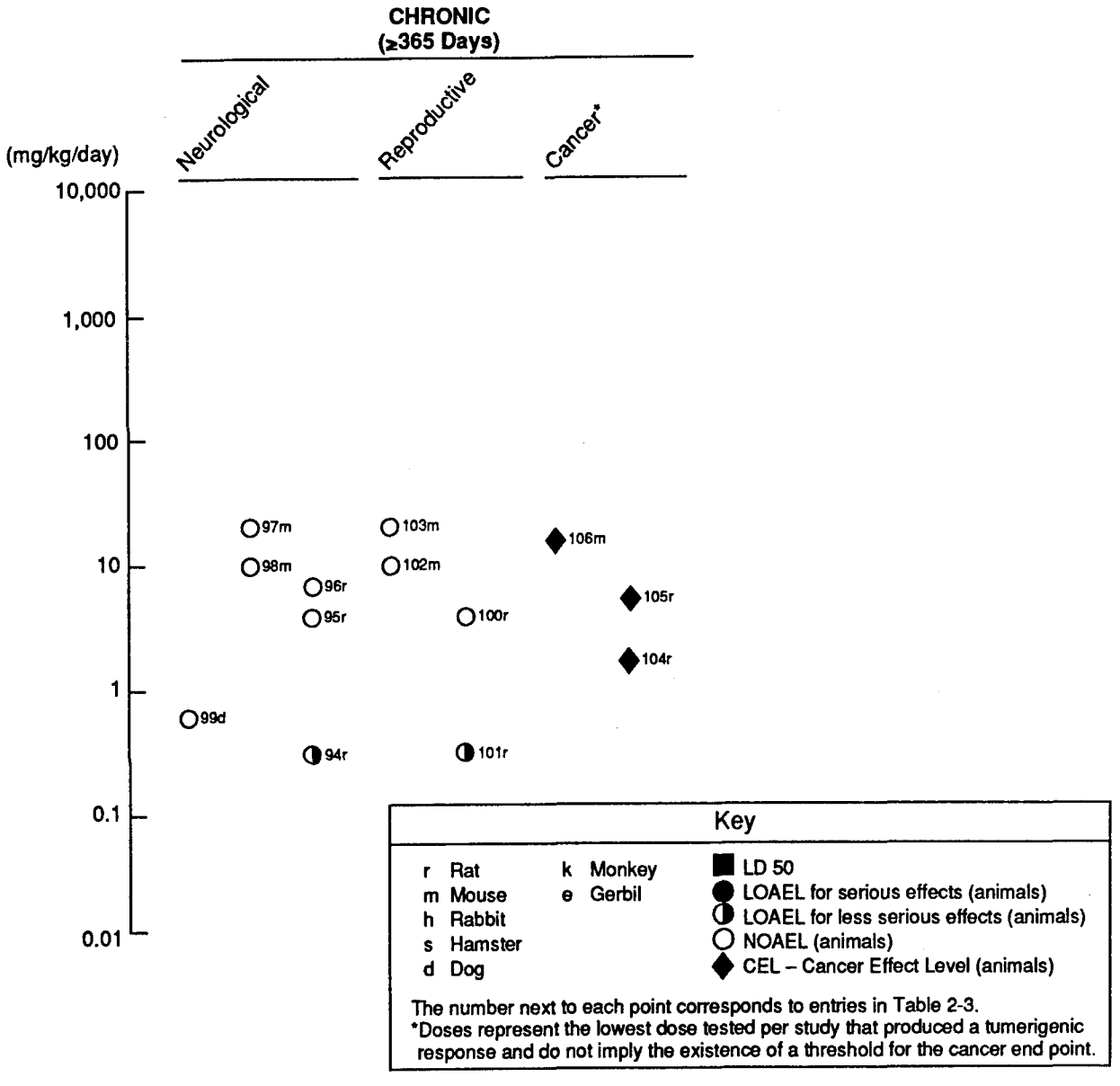


FIGURE 2-3 (Continued)



In intermediate-duration studies (4 or 13 weeks), rats were fed various inorganic tin compounds. A single female (l/10) died during week 11 with a dose of 795 mg tin/kg/day stannous chloride. A total of four males receiving doses of 315 mg/kg/day died during weeks 8 and 9 leading to discontinuation of this dose (De Groot et al. 1973).

The results of the chronic bioassays showed somewhat lower survival of high dose male rats (63 mg tin/kg/day as stannous chloride) compared to the controls. The data in mice showed survival of control males was affected more than the dosed groups (82 and 164 mg tin/kg/day), but survival of the female dosed groups was affected less than the controls (NTP 1982).

The highest NOAEL values and the reliable LOAEL values for lethality in rats and mice in each duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Organotin Compounds. The oral administration of a proprietary drug, Stalinon, resulted in the deaths of about 100 people in France from an estimated 1,000 who had been treated for osteomyelitis, anthrax, and acne. Most of the 10 or more accounts of this 1954 tragedy are published in the French literature but an excellent summary is provided by the World Health Organization (WHO 1980). The primary ingredients in Stanelon were diethyltin diodide (15 mg/capsule) and linoleic acid (100 mg/capsule). It has been proposed that the deaths were caused by triethyltin iodide which was present as an impurity from the manufacturing process. An estimate of 70 mg of triethyltin has been calculated as the toxic dose for humans ingesting this compound over an 8-day period (Barnes and Stoner 1959). However, too many confounding variables in the reporting of this tragedy limit the interpretation of this calculation. Other than the Stalinon incident, no studies were located regarding deaths in humans after oral ingestion of organotin compounds.

There are publications which provide listings of oral LD_{50} values in animals for hundreds of mono-, di-, and triorganotin compounds (Smith 1978; WHO 1980). Lethal doses for monoorganotins ranging from 1,500 to more than 6,000 mg/kg have been reported for rodents (Pelikan and Cerny 1970). This indicates a low level of toxicity.

For diorganotins, a range of lethal doses of 200-3,750 mg/kg is provided from rodent data (Calley et al. 1967; Pelikan and Cerny 1970). A dose of 50 mg/kg/day dibutyltin dichloride for 3 days caused deaths in 30%-50% of the treated rats. Some deaths occurred in 6-10 days following dosing and were attributed to extensive injury to the bile duct and liver (Barnes and Magee 1958). The specific estimates of acute oral toxicity in these reports suggest that both the mono- and dialkyltins show less toxicity as the chain lengths are increased.

The triorganotin compounds are more acutely toxic than are the mono- and diorganotins based on the oral LD_{50} values. A representative range of lethal dose values in rodents is 10-194 mg/kg body weight (Elsea and Paynter 1958;

Pelikan and Cerny 1969). Oral LD_{50} values for rats have been reported to be 14 mg/kg body weight dimethylethyltin and 7.5 mg/kg body weight methyldiethyltin (Aldridge et al. 1987). Animal data on the acute oral toxicity of the trialkyltins tend to support implication of triethyltin toxicity in the Stalinon deaths. Deaths were reported at a dose of 4 mg/kg triethyltin in the rat (Luijten and Klimmer 1978). In general, the trimethyl and triethyl compounds are the most toxic of the triorganotin compounds. Information on acute oral toxicity of tetraorganotin compounds is limited.

The highest NOAEL values, all reliable LOAEL values for lethality, and LD_{50} values in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory or musculoskeletal effects in humans or animals after oral exposure to inorganic tin or organotin compounds.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic tin compounds. Similar information is given in Table 2-3 and Figure 2-3 for organotin compounds.

Cardiovascular Effects.

Inorganic Tin Compounds. No studies were located regarding cardiovascular effects in humans after oral exposure to inorganic tin compounds.

In a feeding study in rats, at dietary levels ranging from less than 10 to 315 mg/kg/day as stannous chloride for 13 weeks, relative heart weights of males were higher than those of controls (DeGroot et al. 1973). This effect was not dose-dependent and there were no associated histopathological findings. By itself, the significance of the observation is not clear. In a 4 week exposure to the same doses there were no changes in heart weights.

Organotin Compounds. No studies were located regarding cardiovascular effects in humans after oral exposure to organotin compounds.

There was an absence of cardiovascular effects in rats, mice and dogs administered triphenyltin hydroxide in the diets for periods of from 4 to 104 weeks (NC1 1978b; Sachsse et al. 1987; Tennekes et al. 1989a, 1989b) (see Section 2.2.2.8).

Gastrointestinal Effects.

Inorganic Tin Compounds. No studies were located regarding gastrointestinal effects in humans after oral exposure to inorganic tin compounds. However, there are some accounts of persons who developed

gastroenteritis after ingestion of various foods stored in tin cans (WHO 1980). Doses ranged from 250 to 1,000 mg tin/kg body weight.

Data from studies in animals show that inorganic tin compounds can cause gastrointestinal effects. Slightly distended small and large intestines were observed at necropsy of rats fed diets containing 315-325 mg tin/kg/day as either stannous chloride or stannous orthophosphate for 4 weeks. However, there were no histopathological changes (DeGroot et al. 1973).

In another study, effects on the morphology and on absolute and relative weights of the gastrointestinal tract were evaluated after feeding rats dietary levels of 7.9 and 15.9 mg tin/kg/day stannous chloride for 4 weeks. Feed restriction was also studied in an attempt to distinguish between tin effects and the effects of decreased food intake and poor growth (Jansen et al. 1985). Increased relative weights of stomach, cecum, and colon were observed at the lowest tin dose, but were apparently caused by diminished food intake since these changes were present in the pair fed controls as well as the tin exposed animals. On the other hand, increases in the weight and length of the small intestines were observed to be independent of food consumption and thus a consequence of the exposure to stannous chloride. There was also an increase in the villus length, a decrease in the number of villi per unit surface, an increase in villus cell turnover, and changes in villi morphology in the intestines of the treated rats. Although similar changes of the intestinal villi were reported by Dreef-van der Meulen (1974), there are not enough data at this time to characterize the intestinal changes as adverse.

Mice fed 311-2,457 mg tin/kg/day as stannous chloride for 13 weeks showed gross distention of the cecum and reddened gastric mucosa at necropsy but no compound-related histopathological changes (NTP 1982). Similar findings were observed in rats fed 120-236 mg tin/kg/day (NTP 1982). However, no such changes were observed in rats fed 32 or 63 mg tin/kg/day or mice fed 82 or 164 mg tin/kg/day as stannous chloride during a 105-week study (NTP 1982).

The feeding of stannous chloride at relatively high doses for intermediate durations caused gastrointestinal distress in rats and mice.

Organotin Compounds. No studies were located regarding gastrointestinal effects in humans after oral exposure to organotin compounds.

In studies designed primarily to characterize biliary and hepatic lesions (see discussion on Hepatic Effects below), distention of the rat stomach with fluid was observed 24 hours after dosing with 50 mg/kg body weight dibutyltin dichloride (Barnes and Magee 1958). The duodenum was also examined in many rats, but no changes were evident. In single-dose studies, 500 mg/kg body weight tributyltin salts (chloride, acetate, benzoate, oleate) produced hemorrhages in the digestive tract of mice (Pelikan and Cerny 1968). Similar changes were seen in another study in mice in which single doses of 4,000 mg/kg body weight butyltin trichloride and other salts produced

hyperemic stomachs and intestines and stomachs distended with fluid. Histopathological changes included massive hemorrhages in the stomach and intestines (Pelikan and Cerny 1970). These changes were not seen in 4-week studies in rats fed 320 mg/kg/day bis(tributyltin)oxide in their diets (Krajnc et al. 1984). Except for the Barnes and Magee (1958) study, the information derived from the studies is difficult to evaluate in view of the high doses utilized.

Hematological Effects.

Inorganic Tin Compounds. No studies were located regarding hematological effects in humans after oral exposure to inorganic tin compounds.

Data from 4-week feeding studies in rats showed some hematological changes (DeGroot et al. 1973). A significant increase was observed in the hematocrit of male rats fed a dietary level of 395 mg tin/kg/day as stannous sulfide but not in females. Both sexes of rats fed tin at dietary levels ranging from 68 to 325 mg tin/kg/day as the chloride, orthophosphate, sulfate, oxalate, and tartrate showed anemia. The signs of the anemia were decreased hematocrit, total erythrocytes, and hemoglobin levels. Lower mean corpuscular volume and hemoglobin concentrations were seen at the highest doses (225-325 mg tin/kg/day). In 13-week studies, stannic oxide produced no hematological changes in rats (DeGroot et al. 1973). However, dietary levels of 7.6 mg tin/kg/day or greater as stannous chloride, produced decreased hematological values in rats with 4-13 week exposures (Dreef-van der Meulen et al. 1974; DeGroot et al. 1973; Janssen et al. 1985). It is possible that diet had an effect on the results of these studies since the no effect levels (22-440 mg Sn/kg/day) for hematological effects in studies using diets adequate in copper and iron (De Groot et al. 1973; Dreef-van der Meulen et al. 1974) exceeded the LOAEL (7.9 mg/kg/day) from the work by Jansen et al. (1985) using diets which contained only one fifth as much. Iron and copper are key nutrients in hematopoiesis; deficiencies in these elements are associated with microcytic anemias characterized by low hemoglobin and hematocrit values. It is suggested that the poor iron and copper nutriture in the Jansen et al. (1985) work was a predisposing factor which amplified the adverse effects of tin on hematological parameters. This hypothesis is supported by studies in which the dietary concentrations of copper, tin, and iron were varied (De Groot 1973). High levels of copper and iron (well above dietary requirements) added to simipurified diets containing up to 75 mg/kg/day tin prevented hematological changes almost completely.

Organotin Compounds. No studies were located regarding hematological effects in humans after oral exposure to organotin compounds.

Decreased hemoglobin and hematocrit values, lowered mean corpuscular volume and hemoglobin mass, and decreased leucocytes were observed in rats at dietary levels of 80 and 320 mg/kg/day bis(tributyltin)oxide for 4 weeks. Erythrocytes were reduced, and spherocytes and Howell-Jolly body-containing erythrocytes were increased in the 320 mg/kg/day group only. Differential

leucocyte counts were variable (Krajnc et al. 1984). In another study performed in the same laboratory, hematological parameters were monitored at 3, 12, and 24 months in rats fed dietary levels of 0.025, 0.25, and 2.5 mg/kg/day bis(tributyltin)oxide. The only changes occurred after 1 year and consisted of reduced peripheral blood lymphocytes and an increase in platelets in the females fed 2.5 mg/kg/day (Wester et al. 1987). At these reduced dietary levels administered over a long period of time, bis(tributyltin)oxide did not produce significant hematological changes. The results of intermediate-duration studies indicate that bis(tributyltin)oxide produced hematological changes in rats, but at fairly high doses.

There was a significant decrease in hemoglobin concentration in male rats fed 7.5 mg/kg/day di-n-butlytin dichloride for 6 weeks but not in females (Seinen and Williams 1976). There were no changes in circulating lymphocytes in these animals despite atrophy of the thymus.

Triphenyltin hydroxide at a dose of 1.3 mg/kg/day caused a transient decrease in hemoglobin and hematocrit values at 26 and 52 weeks in female rats, but not in the males (Tennekes et al. 1989a). These changes were not apparent at 78 and 104 weeks (Tennekes et al. 1989a), nor were they seen in dogs given the same compound at doses of 0.7 mg/kg/day (Sachsse et al. 1987).

Hepatic Effects.

Inorganic Tin Compounds. No studies were located regarding hepatic effects in humans after oral exposure to inorganic tin compounds.

Hepatic effects have been observed following intermediate and chronic oral exposure of rats. Data from a 4-week feeding study in rats showed some histopathological changes (DeGroot et al. 1973). Both sexes fed tin as the chloride, orthophosphate, sulfate, oxalate, and tartrate had histopathological changes in the liver. The cytoplasm exhibited a clear homogeneous appearance which suggested a disappearance of the cellular organells and impaired cell function at the highest dietary level of 226-325 mg/kg/day and to a lesser extent at a level of 68-98 mg tin/kg/day (the doses vary with the tin compound used). A slight but definite oval cell type hyperplasia of the bile ducts was also apparent. Changes in organ weights were inconsistent. The authors suggested that the changes in liver cell morphology were due, in part, to the reduced food intake and resultant impaired weight gain. These changes were apparent in the animals with the poorest weight gains.

In a 13-week study in rats, histopathological changes were again observed in the livers of both sexes at a dietary level of 315 mg tin/kg/day as stannous chloride, but in only a few rats at a level of 95 mg tin/kg/day (DeGroot et al. 1973). The changes were a homogeneous appearance of the cell cytoplasm and a mild proliferation of the bile duct epithelium. Organ weights were not affected. In another 13-week study, similar changes were seen in the livers of rats fed a diet that was gradually increased to a final level of 252 mg tin/kg/day as stannous chloride (Dreef-van der Meulen 1974).

No hepatic effects were reported in rats and mice fed stannous chloride for either 14 days or 13 weeks (NTP 1982). Highest dietary levels were 236 mg tin/kg/day as stannous chloride for the rats and 2,457 mg tin/kg/day for the mice. Considering the extremely high doses used, it is surprising that hepatic changes were not observed in these studies.

Hepatic changes were limited following chronic oral exposure of rats and mice to stannous chloride. In a drinking water study at 0.7 mg tin/kg/day as stannous chloride for life, 80 rats were evaluated for hepatic and other health effects (Schroeder et al. 1968). There was a significant increase in fatty degeneration of the liver in the tin exposed rats. Although 38% of the control rats exhibited slight to severe liver degeneration, 68% of the tin treated rats were affected. Severe fatty degeneration was present in 55% of the control rats and 65% of those exposed to tin. Although similar hepatic effects were reported in the 105 week chronic bioassay of stannous chloride in rats and mice, the incidence of the findings was not dose-related and essentially comparable in treated and control animals (NTP 1982).

Organotin Compounds. No studies were located regarding hepatic effects in humans after oral exposure to organotin compounds.

Hepatic and bile duct effects were observed following acute- and intermediate-oral exposures of animals to organotin compounds. Severe hepatic injury occurred in rats that died 6-10 days following 3 repeated doses of 50 mg/kg/day dibutyltin dichloride (Barnes and Magee 1958). The main features of the bile-duct injury included thickening, inflammation, and dilatation of the proximal part. Histologically, the epithelium of the wall was replaced by granulomatous. In cases in which the bile duct was perforated, severe peritonitis and fat necrosis were seen. Multiple yellow infarcts developed in different lobes of the liver, followed by inflammation of the portal blood vessels. In some cases there was complete necrosis of the bile ducts. Similar lesions have been reported in mice but not in rabbits or guinea pigs (Barnes and Magee 1958).

In a 4-week feeding study in rats, it was only at dietary levels of 320 mg/kg bis(tributyltin)oxide that a low incidence of liver and bile duct changes were observed (Krajnc et al. 1984). The changes included atrophy of hepatocytes, necrotic areas (nonlobular), and bile duct hyperplasia.

Liver changes in rats, mice, and hamsters appear to be secondary to the injury to the bile ducts presumably caused by either the di- or tributyltin compounds (Barnes and Magee 1958; Jang et al. 1986). These animals have common bile-duct systems. In rabbits and guinea pigs that have separate bile duct systems hepatic lesions were not observed, suggesting that bile duct structure may influence susceptability to hepatic damage.

A dose-related trend towards portal sclerosis and bile duct . proliferation was observed in rats given doses of from 0.3 to 6.2 mg/kg/day triphenyltin hydroxide for 52 and 104 weeks; there was no corresponding increase in liver weight (Tennekes et al. 1989a). The dose-related trend was

stronger in females ($p<0.005$) than in males ($p<0.005$). In mice this same compound was associated with a 35%-40% increase in liver weight and nodular hyperplasia at doses of 15.2 mg/kg/day for males and 20.2 mg/kg/day for females but not at lower doses (Tennekes et al. 1989b).

Renal Effects.

Inorganic Tin Compounds. No studies were located regarding renal effects in humans after oral exposure to inorganic tin compounds.

Various renal effects have been observed in animals after oral exposure to inorganic tin compounds.

Histopathological changes in the kidneys were reported for rats which had received dietary levels up to 315 mg tin/kg/day as stannous chloride for 13 weeks (DeGroot et al. 1973). The changes included large protein-like droplets in renal tubular epithelial cells. This appears to be a common finding in the strain of rats used in this study and did not appear to be related to tin exposure. The authors also mentioned the absence of calcareous deposits in the high-dose level female rats. This appears to be an unusual finding since these deposits are usually seen with the species of rats used in the study. However, the relevance of these kidney findings is not clear.

In another 13-week study, rats that were fed the compound up to a maximum level of 252 mg tin/kg/day as stannous chloride, showed increased relative kidney weights (Dreef-van der Meulen 1974). The protein-like droplets and calcareous deposits which are common in the rat strains used were present in the controls but were not seen in the tin-fed animals. The absence of calcareous deposits in the females confirms the observations of DeGroot et al. (1973), but the relevance of these finding to compound toxicity is unclear. The organ weight change itself, in the absence of histopathological or other effects, cannot be considered a toxic effect.

Renal changes have been evaluated following chronic oral exposure of rats and mice to stannous chloride. The studies involved here have been described under Hepatic Effects. Vacuolar changes in the proximal convoluted tubules of the kidney were significantly increased in rats administered stannous chloride as compared with controls (Schroeder et al. 1968). However, in 14 day, 13 week, and 105 week studies of stannous chloride in rats and mice, no treatment-related nonneoplastic renal changes were reported (NTP 1982).

Organotin Compounds. No studies were located regarding renal effects in humans after oral exposure to organotin compounds.

When tributyltin laureate was administered as a single high dose (4,000 mg/kg) to mice, gross renal changes were observed at necropsy of the animals 24 hours later. The kidneys were light red and slightly enlarged. Similar findings, accompanied by small hemorrhages on the renal capsules, were observed in mice administered trimethyltin oleate (Pelikan and Cerny 1970).

Histopathological findings included steatosis of the renal cortical tubular epithelium and hyperemia of the renal medulla. Because these renal changes resulted from single high doses of the compounds, kidney toxicity was suggested.

In a more definitive study of kidney toxicity, water consumption and urine production were measured for 3 days in rats administered 3, 6, and 10 mg/kg body weight tributyltin chloride by gavage. Acute effects were slightly dilated tubules and increased urine volume and pH, apparently caused by the low concentrations of the compound circulating in the blood. Water consumption was increased. Relative kidney weights were increased in both the 6- and 10-mg/kg body weight groups. Various histopathological changes were seen in all dose groups, but the most important appears to be the marked necrosis of the proximal tubules seen only at 10 mg/kg body weight dose (Opacka and Sparrow 1985). This finding corresponds to the observations of Rey et al. (1984) who described shock kidneys (i.e., proximal tubule degeneration) in a patient who died from trimethyltin poisoning (see Section 2.2.1.1).

Kidney toxicity and pathology were studied in detail following administration of single oral doses of 12.25 mg/kg body weight trimethyltin chloride to rats (Robertson et al. 1987). This was an attempt to define each stage in the development of kidney changes and determine if the changes correlate with the fairly well-known neurotoxicity of trimethyltin (see Section 2.2.2.4). The results of this study were essentially in agreement with the Opacka and Sparrow (1985) findings of marked proximal tubular damage, increased urinary pH, and polyuria. This study characterized over a 14-day observation period the step-wise development of the kidney pathology along with other pertinent aberrations such as increased blood urea nitrogen levels. The data suggest that the most severe kidney toxicity occurs at 7-11 days following dosing. Body weight loss and neurobehavioral changes in the rats accompanied the development of the kidney changes.

Triphenyl tin hy'droxide did not induce alterations in kidney structure or function in rats, or dogs given doses of 0.07-6.2 mg/kg/day for up to 104 weeks (Sachsse et al. 1987; Tennekes et al. 1989a). There were no changes in kidney weight or nor did any of the biochemical indices of kidney damage (blood urea nitrogen, electrolyte levels, urinary protein) suggest that kidney function had been altered. Histopathological examination of the kidney did not reveal any compound related abnormalities. In mice there was a 6%-8% decrease in the kidney to body weight ratio without accompanying histopathological damage in males with doses of 3.5 and 15.2 mg/kg/day as triphenyltin hydroxide administered over an 80-week period (Tennekes et al. 1989b).

Dermal/Ocular Effects.

Inorganic Tin Compounds. No studies were located regarding dermal or ocular effects in humans or animals after oral exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding dermal or ocular effects in humans after oral exposure to organic tin compounds.

In female mice, a dose of 20.2 mg/kg/day triphenyltin hydroxide administered for 80 weeks as associated with dermal sores and burn-like lesions, and was sometimes accompanied by hair loss (Tennekes et al. 1989b). These lesions were present primarily in the back cervical area but were also identified on the head, ears, forelimb and abdomen. Males were affected to a much lesser extent than the females. No skin lesions were associated with the administration of triphenyltin hydroxide to rats or dogs (Sachsse et al. 1987; Tennekes et al. 1989a).

Other Systemic Effects.

Inorganic Tin Compounds. Reductions in body weight, food intake, and water consumption were observed in oral studies of inorganic tin compounds. Decreases in body weights and reduced food intake were recorded in studies in which stannous chloride and other inorganic tin compounds were administered to rats for acute and intermediate-durations (DeGroot et al. 1973; Dreef-van der Meulen 1974; Janssen et al. 1985). However, these parameters were comparable between control and treated rats fed stannous chloride during chronic studies (Schroeder et al. 1968; NTP 1982). The findings appear to suggest direct action of some inorganic tin compounds on growth and food intake after acute and intermediate-duration dosing but not during chronic dosing.

Organotin Compounds. Decreased body weights, reduced food intake, and reduced water consumption were observed after oral administration of bis(tributyltin)oxide to rats in acute and intermediate studies (Elsea and Paynter 1958; Krajnc et al. 1984) and chronic studies (Wester et al. 1987). Triphenyltin hydroxide was also associated with reduced body weights and food intake in rats and a reduced body weight in mice when compared with controls (Tennekes et al. 1989a, 1989b). It appears that these organotin compound produced decreased body weights and food and water consumption on oral studies of any duration.

Function and pathological changes of the endocrene system were evaluated in a detailed intermediate study in which rats were fed 20 and 80 mg/kg/day bis(tributyltin)oxide for 6 weeks (Krajnc et al. 1984). In this study concentrations of serum insulin, thyroxin, and thyrotropin decreased. Luteinizing hormone was increased at the high level. No changes were measured in concentrations of follicle-stimulating hormone and corticosterone. Histopathology confirmed the functional changes. For example, the epithelial lining of the thyroid follicles was flattened indicating a low level of activity in this organ.

In contrast to the results reported in the intermediate-duration study, no major endocrine function changes were noted in rats fed is(tributyltin)oxide for 2 years (Wester et al. 1987).

Triphenyltin hydroxide caused dose-related cystoid changes in the pars intermedia of the pituitary gland for male and female mice administered this compound for 52 or 104 weeks at doses of 0.3-6.2 mg/kg/day (Tennekes et al. 1989a). Up to 40% of the males and 80% of the females were affected at 52 weeks by the highest dose. At the end of 104 weeks, 72.3% of the high dose males and 55.6% of the females exhibited the cystoid changes. The lower incidence in females at 104 weeks related to a high early mortality from fatal pituitary adenomas (see Section 2.2.2.8).

2.2.2.3 Immunological Effects

Inorganic Tin Compounds. No studies were located regarding immunological effects in humans and animals after oral exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding immunological effects in humans after oral exposure to organotin compounds.

Studies of acute and intermediate duration have demonstrated the specific action of organotin compounds on the immune system of animals after oral exposure. Dose-related decreases in the weights of the thymus, spleen, and lymph nodes were observed in rats fed dietary levels of 0, 2.5, and 7.5 mg/kg/day dialkyltin compounds for 2-6 weeks (Seinen et al. 1977b; Seinen and Williams 1976). Progressive atrophy of the thymus tissue including a decrease in the number of cells and cell viability were apparent at both tested dose levels with di-n-octyltin dichloride. There was also a doserelated decrease in cortical lymphocytes (Seinen and Williams 1976). Lymphoid atrophy did not occur in mice. Similar organ atrophies were produced in rats gavaged with a single dose (100 mg/kg bis(tributyltin)oxide) and repeated administration studies. Dose levels were 3, 6, and 12 mg/kg/day, 5 days per week for 13 or 26 weeks (Funahashi et al. 1980).

Bis(tributyltin)oxide was used in two more detailed studies intended to further characterize immunological effects in animals. In rats fed up to 320 mg/kg/day bis(tributyltin)oxide in the diet for 4 weeks, thymus atrophy and dose-related severe lymphocytopenia of the thymus cortex and depletion of T-lymphocytes in the spleen and mesenteric lymph nodes were reported (Krajnc et al. 1984). Other findings included rosettes of erythrocytes that were found around mononuclear cells in the medullary sinuses of mesenteric lymph nodes. The authors regarded this to be the most sensitive parameter; however, the underlying mechanism is not clear. Perhaps hemorrhages in the intestinal tract drained by these lymph nodes were involved. However, the hemorrhages were not seen histopathologically.

In a second study of intermediate duration (6 weeks), weanling rats were fed dietary levels of 0, 20, and 80 mg/kg/day bis(tributyltin)oxide (Krajnc et al. 1984). The expected decreased organ weights and lymphocytopenia were seen. Suppression of thymus-dependent immunity was produced as shown by depressed delayed-type hypersensitivity reactions and reduced response of the thymus and spleen cells to T-cell mitogens due to reduced numbers of T-cells.

Natural killer activity was decreased in the spleen. This observation was confirmed by Van Loveren et al. (1990). This was particularly true at the 80 mg/kg/day level. The effects produced by bis(tributyltin)oxide appear to be due to direct action of the compound on the lymphocytes in the thymus since cell damage was seen.

The suppression of the immune system has also been demonstrated in a study in which rats were fed dietary levels of 0.025, 0.25, and 2.5 mg/kg/day bis(tributyltin)oxide for 15 months (Wester et al. 1987). The specific results were similar to findings in the intermediate-duration studies. Based on the reduction of both cellular immune responses and nonspecific immunity, a NOAEL of 0.5 tin/kg/day is suggested by the authors.

The immunological effects of bis(tributyltin)oxide were further investigated in comparative studies of adult and pre-weanling rats (Smialowicz et al. 1989). Several immune parameters were altered in rats exposed to 10 daily doses (1.25-10 mg/kg/day) bis(tributyltin)oxide or intermittent doses (3x/week) for a total of 10 doses at 5, 10, or 20 mg/kg/day bis(tributyltin) oxide. The changes included a reduction in thymus weights and suppression of lymphoproliferative (LP) responses for different T-cell mitogens. Similarly, immune parameters were altered in pre-weanling rats (beginning at 3 days of age) exposed to a total of 10 doses (2.5, 5, or 10 mg/kg/day bis(tributyltin)oxide) over a 24-day period. Reduced thymus weights, increased spleen weights, reduced natural killer cell activity, and reduced LP responses were observed at the 5 or 10 mg/kg/day levels. The data indicated that the immune responses occurred in young rats at doses lower than those that produced similar responses in adult rats. The pre-weanling rat is, therefore, more sensitive to bis(tributyltin)oxide than is the adult rat.

Triphenyltin hydroxide also appeared to have an effect on immunity in both rats and mice. In rats, the effect was transitory as reflected in slight to moderate changes in the immunoglobins IgG, IgA, IgM in both males and females at 50 weeks but not at 80 weeks (Tennekes et al. 1989a). At doses of 0.3-6.2 mg/kg/day, levels of IgGl and IgG2a were moderately reduced in females, while the levels of Ig2c and IgA were decreased in the males. There was a moderate increase in IgM values for males and females at the two highest dose levels.

In mice there were slight to moderate decreases in the levels of IgG, IgA, and IgM in males and females exposed to 15.2 and 20.2 mg/kg/day triphenyltin hydroxide for 80 weeks. Increases in the relative numbers of lymphoid cells, were found in the femoral bone marrow myelograms of all of the exposed animals but there were no observed differences in the peripheral blood lymphocytes and monocytes. It is, accordingly, difficult to evaluate the clinical significance of the bone marrow tests.

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3 for organotin compounds.

2.2.2.4 Neurological Effects

Inorganic Tin Compounds. No studies were located regarding neurological effects in humans after oral exposure to inorganic tin compounds.

In the studies of systemic and other effects of inorganic tin compounds in animals (Sections 2.2.2.1 and 2.2.2.2), clinical signs of neurotoxicity or behavioral changes were surprisingly not noted. However, central nervous system effects in animals consisting of ataxia, muscular weakness, and depression have apparently been associated with oral exposure to the inorganic compounds (WHO 1980). Histopathological examinations of rats fed levels of 315 mg tin/kg/day as stannous chloride for 8-9 weeks revealed a spongy state of the white matter of the brain (DeGroot et al. 1973). However, the treatment of these animals was terminated at 9 weeks because of the number that were dead or moribund. It is, accordingly, difficult to determine if the tissue changes observed are due to compound administration or the poor physiological status of the animals. There were no other neurological changes reported and the meaning of the finding is not clear.

Organotin Compounds. Death and intoxication resulting from the Stalinon incidents are described in Section 2.2.2.1. Stalinon contained diethyltin diodide and undetermined amounts of triethyltin iodide. It has been hypothesized that the neurotoxic effects of this preparation were due to the tributyltin (WHO 1982). Symptoms in the affected persons appeared suddenly, about 4 days following ingestion of the drug, and included vertigo, intense headache, photophobia, altered consciousness, visual impairment, and convulsions. Sensory disturbances, hypoflexia and loss of sphincter control were common observations. Deaths occurred after 4-10 days as the result of deep coma, or more frequently, acute intracranial hypertension. Autopsies revealed diffuse edema in central nervous system white matter (Foncin and Gruner 1979). Although there is no clear cause and effect relationship between this human organotin exposure and the symptoms observed, the experimental studies discussed below demonstrate that behavioral and morphological changes of the nervous system are associated with exposure to several organotin compounds.

The effects associated with oral exposure of animals to triorganotins (i.e., trimethyltin and triethyltin) have been described in a number of studies. Single or repeated doses of trimethyltin chloride or methacrylate administered by gavage to rats, produced tremors, hyperexcitability, aggressive behavior, weight loss, and convulsions (Brown et al. 1979). The prominent histopathological change was neuronal alterations in the hippocampus. This finding is characteristic of the methyltins. Studies of the brain response to electrical stimulation of selected areas of the brain suggest that reduced inhibition of the mossy fiber system may cause the hippocampal damage through overstimulation of the pyramidal cells (Dyer and Boyes 1984). The behavioral changes produced by the dimethyl compounds generally have a slow onset, are long in duration, and are sometimes irreversible.

Acute studies have also been conducted to assess the neurotoxic effects of trimethyltins in other species. Single doses of 3 mg/kg trimethyltin chloride to mice and 7.5 mg/kg to rats produced tremors and aggression. The signs appeared sooner and the hippocampal lesions were more prominent in mice (Chang et al. 1983). In gavage studies with trimethyltin chloride, hamsters, gerbils, and marmosets exhibited the characteristic signs of toxicity including tremors, ataxia, and aggression. Damage to the hippocampus, pyriform cortex, fascia dentata, and amygdaloid nucleus were produced in this study at doses near the lethal dose for each species: rat (for comparison) -- 12.6 mg/kg trimethyltin chloride; hamsters, gerbils, and marmosets --3 mg/kg (Brown et al. 1984). The authors state that trimethyltin chloride binds to hemoglobin in the rat resulting in less toxicity. Since this binding does not take place in the other three species or in humans, the compound is distributed more quickly to tissues, and greater toxicity is observed. A lethal dose for humans was estimated by the authors to be 3 mg/kg. However, this simple extrapolation may not be warranted; humans may be more highly susceptible to the neurotoxic and lethal effects of the trimethyltins than are these other species.

Triethyltins produce different effects than do trimethyltins. For example, a specific white matter edema and myelin sheath splitting (i.e., the lamellae) in the central nervous system are produced by exposing rats to 2.8 mg/kg/day triethyltin sulfate in the drinking water for 22 days (Graham and Gonatas 1973). Extensive vacuole formation was also a feature of the changes. The signs of toxicity were motor dysfunction and paralysis.

Similar signs of toxicity were observed in male rats exposed to 4.2 mg/kg/day triethyltin bromide for 3 weeks (Richman and Bierkamper 1984). The rats developed hindlimb weakness in week 1 followed by paresis and paralysis by week 3. There was apparent recovery at the end of week 3. The primary histopathological findings were demyelination in the spinal cord, degeneration of axons of the sciatic nerve, and atrophy of fibers of the soleus muscle. This study demonstrated that both nerve and muscular components are involved in producing peripheral motor dysfunction.

In another drinking water study, both single and repeated doses of triethyltin bromide produced performance decrements in a series of behavioral toxicity tests in rats (Reiter et al. 1980). The effects were rapid in onset but reversible 1 month after exposure was discontinued. Such findings correlate well with the effects on the myelin sheath (i.e., demyelination). These changes also illustrate the characteristic effects of the triethyltins as compared to trimethyltins. The authors estimated that a behavioral threshold for the rat is between 8-10 mg/kg/day triethyltin bromide for a 3-week exposure.

It should be noted that the cerebral edema produced by triethyltin can be regarded as a specific effect. However, the lesions of the bile ducts in rats and mice previously described for dibutyltin compounds appear to be a more species-specific effect.

Single gavage doses of tributyltin compounds at extremely high doses (4,000 mg/kg tributyltin acetate, benzoate, chloride, or oleate) to mice resulted in hypoactivity, impaired respiration, and convulsions (Pelikan and Cerny 1970).

The highest NOAEL values and all reliable LOAEL values for neurotoxic effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3 for organotin compounds.

2.2.2.5 Developmental Effects

Inorganic Tin Compounds. No studies were located regarding developmental effects in humans or animals after oral exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding developmental effects in humans after oral exposure to organotin compounds.

Mice were administered 1.2-35 mg/kg/day bis(tributyltin)oxide by gavage on days 6-15 of gestation in order to evaluate both prenatal and developmental effects (Davis et al. 1987). Dose-related decreases in fetal weights were observed with a marked effect (i.e., 20% decrease) at the highest dose level. Some skeletal abnormalities, such as fused ribs and ossification centers in the sternebrae and cleft palates, were seen at all dose levels and also in the controls.

Because of the lack of details for methods used and statistical evaluation of the data, as well as the occurrence of developmental effects in both treated and control animals, it is difficult to attribute the effects, even at the higher doses, to the administration of bis(tributyltin)oxide. Another factor, discussed in Section 2.2.2.6, is the maternal toxicity observed in the studies at dose levels of 23.4 mg/kg/day and above.

Fetal weights were slightly depressed (11%) in the offspring of 22 New Zealand white rabbits that were given 0.9 mg/kg/day triphenyltin hydroxide by gavage during the period of organogenesis (Rodwell 1987). Delayed ossification of the hyoid bone was also present but there were no teratogenic effects. These observations are consistent with the effects on maternal weight discussed in Section 2.2.2.6. There were two spontaneous abortions at the 0.9 mg/kg/day dose which were within the historical norms for the species. However, effects from administration could not be eliminated as a cause for this observation, since there was one abortion in the control and low dose group and none in the medium dose group.

All reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-3 are plotted in Figure 2-3 for organotin compounds.

2.2.2.6 Reproductive Effects

Inorganic Tin Compounds. No studies were located regarding reproductive effects in humans after oral exposure to inorganic tin compounds.

In a 13-week study in rats, dietary levels ranging from 1.5 to 9.2 mg tin/kg/day as stannous chloride, caused testicular degeneration (DeGroot et al. 1973). Histopathological degeneration was seen in a few animals who were treated for 9 weeks with 30.5 mg/kg/day and then sacrificed because of their moribund physiological state. The meaning of the findings is not clear.

Organotin Compounds. No studies were located regarding reproductive effects in humans after oral exposure to organotin compounds.

The pregnant mice administered bis(tributyltin)oxide, as described in Section 2.2.2.5, showed some maternal toxicity at the doses used in the study (Davis et al. 1987). One of the six mice at the highest dose (35 mg/kg/day bis(tributyltin)oxide) died, and there was a high rate of resorptions. One of five litters was completely resorbed. Decreases in maternal weight gain were greatest at this level with only slight decreases observed at the other doses. The developmental effects were most prominent at the high dose level, and were most likely secondary to the maternal toxicity.

New Zealand white rabbits administered doses of 0.3 and 0.9 mg/kg/day as triphenyl tin hydroxide by gavage during the period of organogenesis failed to gain weight at the same rate as the controls or the animals given 0.1 mg/kg/day. Food consumption was also reduced (Rodwell 1987). Male rats fed this same compound at doses of 0.3 mg/kg/day and above displayed a doserelated increase in Leydig cell hyperplasia ($p<0.0005$) and tubular atrophy ($p=0.004$) of the testes (Tennekes et al. 1989a) which was not seen in either rats or mice fed 3.75 mg/kg/day for 78 weeks (NC1 1978b).

Female rats fed 3.33 mg/kg/day and 6.65 mg/kg/day dibutyltin diacetate demonstrated inflammation and hyperplasia of the uterus. The frequency with which these changes were observed was greater in the low dose group than in the high group (NCI 1978a). However, the tissues from 17 of the 50 high dose group animals were lost before microscopic examination. Thus, caution must be used in interpreting these results. A low incidence of uterine cysts (9-12%) but no inflammation was present in mice given 9.9 or 19.8 mg/kg/day for the same duration (NC1 1978a).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration are recorded in Table 2-3 and plotted in Figure 2-3 for organotin compounds.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans and animals after oral exposure to inorganic tin or organotin compounds.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

Inorganic Tin Compounds. No studies were located regarding cancer effects in humans after oral exposure to inorganic tin compounds.

A carcinogenesis bioassay for stannous chloride was conducted in male and female rats and mice. Diets containing 32 or 63 mg tin/kg/day as stannous chloride were fed to rats and 82 or 164 mg tin/kg/day to mice for 105 weeks (NTP 1982). Aspects of the toxicity of stannous chloride observed during prechronic studies completed prior to the bioassay have been presented in Sections 2.2.2.1 and 2.2.2.2. Tumors occurred at increased incidences in the dosed groups in the bioassay. These included C-cell adenomas of the thyroid in low-dose male rats, lung adenomas in the high-dose male rats, hepatocellular adenomas and carcinomas and histiocytic lymphomas in both lowand high-dose female mice. However, the authors concluded that the incidences of the tumors relative to the histological control rat and mouse data were similar and not clearly related to administration of stannous chloride. The possibility that the C-cell tumors in the thyroid may have been related to stannous chloride feeding was not ruled out since the incidence in the low dose group but not the high dose group is significant with comparison to the controls and historical controls. Despite the reservation the conclusion from the NTP (1982) data was that stannous chloride was not carcinogenic for male or female rats or mice under the experimental conditions of the study.

An earlier chronic oral study that evaluated the carcinogenic potential of sodium chlorostannate must be regarded as flawed for several reasons. The rats were fed on irregular dose schedules and most of the animals developed pneumonia (Roe et al. 1965). After 1 year, three malignant tumors were identified in 30 rats, Long-term chronic studies of stannous chloride in rats and mice were conducted using a single low dose exposure and limited pathology studies (Schroeder and Balassa 1967; Schroeder et al. 1968). The authors concluded that stannous chloride was not carcinogenic.

Organotin Compounds. No studies were located regarding cancer effects in humans after oral exposure to organotin compounds.

A carcinogenesis bioassay for dibutyltin diacetate was conducted in male and female rats and mice (NCI 1978a). Rats received dietary levels of 3.33 or 6.65 mg/kg/day dibutyltin diacetate for 78 weeks followed by a period of no compound administration for 26 weeks. Mice also received the compound in the diet at dosage levels of 9.9 or 19.8 mg/kg/day for 78 weeks followed by a period of no compound administration for 14 weeks. Evaluation of this study was based largely on statistical tests of treated versus control data. There were generally no significant differences indicated such as with the hepatocellular adenomas observed in male and female mice. However, there was an important problem with the study, namely, the loss of tissues from 17 high dose female rats. This prevented an evaluation of uterine neoplasms some of which had been seen in the low level female rats. Apparently there were no

historical control data available at the time for evaluation of background versus experimental findings. The general conclusion was that dibutyltin diacetate was not carcinogenic for male rats and male or female mice under the experimental conditions of the study. The loss of the tissues prevented reaching a conclusion with regard to the relationship between dibutyltin diacelate and the occurrence of uterine neoplasms in female rats.

Another organotin compound, triphenyltin hydroxide, was tested in a bioassay using male and female rats and mice (NC1 1978b). The regimen included dietary feeding for 78 weeks followed by a 26-week observation period. Dosage levels were for rats: 1.88 and 3.75 mg/kg/day as triphenyltin hydroxide and for mice: 4.88 and 9.75 mg/kg/day. Survival was affected in male mice but no other effects were observed in the mice or the rats. Tumors seen in treated animals were comparable to controls. Historical control data were apparently not available at the time for evaluation of background versus experimental findings. The general conclusion was that triphenyltin hydroxide was not carcinogenic for male and female rats and mice under the experimental conditions of the study.

In contrast to these results, longer-term studies of the carcinogenicity of triphenyltin hydroxide in rats and mice, using higher maximum doses, produced tumors in both species (Tennekes et al. 1989a, 1989b). In rats administered doses of from 0.3 to 6.2 mg/kg/day triphenyltin hydroxide in the diet, there was a dose-related increase in pituitary adenomas in the exposed females at 104 weeks. Although the incidence of this lesion was high in the control animals (64.4%), it was even greater in the exposed animals especially at the two highest dose levels (76.8% and 93.1%, respectively). There was also a dose-related decrease in survival for the females which was related to the tumor incidence. Only 23% of the females receiving the highest dose were alive at the termination of the study as opposed to 80% of the males.

The numbers of males with testicular Leydig cell tumors was increased in animals exposed to 5.2 mg/kg/day triphenyltin hydroxide for 104 weeks (16.7% as opposed to 1.7% in the controls).

Tumors were also present in mice given diets containing 0.9-20.2 mg/kg/day triphenyltin hydroxide. After sacrifice at 80 weeks, examination of the tissue revealed an increased incidence of hepatocellular adenomas in both sexes. These tumors were consistent with the nodular hyperplasia seen in the livers of the treated animals. As was the case with the rat study, the females appeared to be more sensitive than the males. There was decrease in survival for the females at the highest dose. Only 50% of the females receiving this dose were alive at the termination of the study as opposed to 70% of the males in the same dose group and 74% of the female control animals.

In a combined toxicity and carcinogenicity study, rats were fed diets containing 0.025, 0.25, and 2.5 mg/kg/day bis(tributyltin)oxide for 106 weeks (Wester et al. 1987). An increased incidence of some benign tumors was observed in both sexes of the high dose level rats. Included were interior

pituitary adenomas (prolactinomas) and pheochromocytomas in the adrenal medulla. In males only, adrenal cortical adenomas were decreased and parathyroid adenomas were increased at this high level. In females only, adenocarcinomas of pancreatic origin accompanied by metastases, were seen. The authors concluded that their results could not be considered evidence of carcinogenicity but that the changes may be related to a direct action of bis(tributyltin)oxide on the endocrine glands. Until complete details of this study are provided, it will not be possible to make an appropriate evaluation of the data presented in the preliminary report of the findings.

2.2.3 Dermal Exposure

Except for dermal/ocular effects (Section 2.2.3.2) there is no information that describes health effects in humans or animals after dermal exposure to inorganic tin or organotin compounds. Table 2-4 summarizes available quantitative information on health effects that have been observed in animals after dermal exposure to organotin compounds.

2.2.3.1 Death

Inorganic Tin Compounds. No studies were located regarding death in humans or animals after dermal exposure to inorganic tin compounds.

Organotin Compounds. The death of a female worker accidentally drenched in phenyltin and other unidentified compounds was described in Section 2.2.1.1. Second and third degree burns developed 12 hours following the accident (NIOSH 1976).

There is a listing of dermal LD_{50} values in animals for a number of organotin compounds (Smith 1978). A dermal LD_{50} in rabbits was reported to be 11,700 mg/kg bis(tributyltin)oxide (Elsea and Paynter 1958). For rats, an LD_{50} of 605 mg/kg is given (Smith 1978). Despite variations in values for other compounds such as benzoates, naphthenates, and fluorides, the acute dermal toxicity of organotin compounds is generally less than by the oral route. The LD_{50} values. for representative species in the acute- and intermediate-duration category are recorded in Table 2-4. Doses are expressed as mg/kg/day compound rather than as doses of tin.

2.2.3.2 Systemic Effects

Inorganic Tin Compounds. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans after dermal exposure to organotin compounds.

TABLE 2-4. Levels of Significant Exposure to Organotin Compounds - Dermal

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE							
Death							
Rat	1 d 1x/d				605 (LD50)	Smith 1978	$C_{24}H_{54}OSn_2$
Rabbit	1 d 1x/d				11700 (LD50)	Elsea and Paynter 1958	$C_{24}H_{54}OSn_2$
INTERMEDIATE EXPOSURE							
Death							
Rabbit	90 d 5d/wk 7hr/d				68 (7/10 animals died)	Sheldon 1975	$C_{12}H_{27}FSn$
Gn Pig	50 d 1x/d				40 (LD50)	Mori et al. 1984	$C_{24}H_{54}OSn_2$
Systemic							
Rabbit	90 d 5d/wk 7hr/d	Derm/oc	14			Sheldon 1975	$C_{12}H_{27}FSn$
Gn Pig	50 d 1x/d	Renal			10 (tubule degeneration)	Mori et al. 1984	$C_{24}H_{54}OSn_2$
		Other		10 (decreased body weight)	40 (severe decrease in body weight)		

$C_{12}H_{27}FSn$ = tributyltin fluoride; $C_{24}H_{54}OSn_2$ = tributyltin oxide; d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s)

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and hepatic effects in animals after dermal exposure to organotin compounds.

Renal Effects. Doses of 10 or 40 mg/kg/day bis(tributyltin)oxide were applied to the shaved skin of male guinea pigs at doses of 10 or 40 mg/kg/day for 50 days (Mori et al. 1984). Swelling, degeneration, and destruction of tubular epithelium was observed but there were no changes in the glomerulus. There was also an increased excretion of sodium, chloride, phosphate, glucose, and amino acids in the urine but decreases in phosphate and amino acids in the serum. According to the authors, these findings constitute a secondary Fanconi syndrome. These renal tubular changes are similar to those seen with inorganic tin compounds after oral exposure (see Section 2.2.2.2) and suggest that the compound was absorbed systemically.

The highest NOAEL value for rabbits and a reliable LOAEL value for guinea pigs in the intermediate-duration category is recorded in Table 2-4.

Dermal/Ocular Effects.

Inorganic Tin Compounds. No studies were located regarding dermal/ocular effects in humans after dermal exposure to inorganic tin compounds.

Stannous fluoride (0.25 and 0.5%) and stannous chloride (1 and 2%) produced leukocyte pustules in rabbit skin along the area adjacent to an abdominal epidermal scratch. Infiltration of the tissue with polymorphonuclear and mononuclear leukocytes were present in the absence of pustules at a stannous chloride concentration of 0.5% and a stannous fluoride concentration of 0.1%.

Organotin Compounds. In contrast to the inorganic tin compounds, there is more information available for organotin compounds from acute and intermediate dermal exposure studies in humans and animals.

It is known that organotins are both skin and eye irritants in humans (Sheldon 1975). Direct skin contact with triphenyl fluoride produced an irritant contact folliculitis in a male worker (Andersen and Petri 1982). Patch tests were performed in human subjects, as well as in guinea pigs and rabbits, but the dermatitis could not be reproduced. An irritant contact dermatitis was also seen in workers using a paint containing bis(tributyltin) oxide (Goh 1985). An earlier study had shown that bis(tributyltin)oxide severely irritated human skin and also produced a contact folliculitis (Lyle 1958). Sensitization was not observed in any of the referenced studies nor in a separate study of bis(tributyltin)oxide-based paints (Gammeltoft 1978). Eyes accidentally splashed with bis(tributyltin)oxide showed lacrimation and intense conjunctival changes. These studies illustrate that skin and eye damage may result from dermal exposure of humans to organotin compounds.

Animal studies tend to confirm the dermal/ocular effects reported for humans. Bis(tributyltin)oxide is a severe irritant to the skin and an extreme eye irritant in rabbits (Sheldon 1975). By contrast, tributyltin fluoride and triphenyltin fluoride produced only minimal skin irritation but were also extreme eye irritants (Sheldon 1975). Other acute studies have likewise demonstrated the skin irritating potential of bis(tributyltin)oxide and triphenyltin acetate in rats (Klimmer 1969; Pelikan and Cerny 1968).

In a 90-day repeated dose dermal study, rabbits developed skin irritation at each of three levels tested (14, 27, and 68 mg/kg/day tributyltin fluoride) (Sheldon 1975). Deaths occurred in 7 of 10 rabbits at a level of 68 mg/kg, but surviving animals eventually returned to normal a few days after compound was withdrawn. A level of 14 mg/kg (65 applications) was stated by the authors to be a NOAEL despite local irritation at the application sites. In view of the exaggerated daily contact with the rabbit skin, this value seems reasonable since such high levels of daily exposure would not be the case in humans. However, a detailed report of this study was not available for review.

A guinea pig study also confirmed the human experience that bis(tributyltin)oxide does not produce sensitization (Schweinfurth and Gunzel 1987).

No studies were located regarding the following effects in humans or animals after dermal exposure to inorganic tin or organotin compounds:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to inorganic tin or organotin compounds.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

Inorganic Tin Compounds. No studies were located regarding cancer effects in humans or animals after dermal exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding cancer effects in humans after dermal exposure to organotin compounds.

In a limited evaluation of carcinogenicity, tributyltin fluoride was applied to the shaved backs of male white mice 3 times per week for a period of 6 months. Treated mice received 15 mg of 5% or 10% of the compound in propylene glycol. Hyperplastic skin changes were observed in the 5% but not

in the 10% group (Sheldon 1975). Carcinogenic effects were not observed in this study, which was only of intermediate duration. No other studies were located regarding cancer effects in animals after dermal exposure to organotin compounds.

2.3 TOXICOKINETICS

2.3.1 Absorption

The results of toxicity studies suggest that inorganic tin compounds are not readily absorbed after oral or inhalation exposure and show only limited effects after dermal exposure. Organotin compounds are more readily absorbed by these three routes of exposure.

2.3.1.1 Inhalation Exposure

Inorganic Tin Compounds. No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to organotin compounds.

2.3.1.2 Oral Exposure

Inorganic Tin Compounds. No studies were located regarding absorption in humans after oral exposure to inorganic tin compounds.

In animals, data suggest inorganic tin compounds are not readily absorbed. At 48 hours after oral administration of ^{113}Sn (a gamma-ray emitting radionuclide), approximately 95% or more of the administered radioactivity was recovered in feces, with 1% or less in urine (Hiles 1974). The various forms of tin (^{113}Sn) compounds administered were stannous pyrophosphate ($Sn_2P_2O_7$), stannous fluoride (SnF_2), stannic fluoride (SnF_4), stannous citrate (Sn[II]citrate), and stannic citrate (Sn[IV]citrate). The absorption of Sn [II] from the gastrointestinal tract was reported to be 2.85% in rats, while 0.64% of the administered Sn [IV] was absorbed (Hiles 1974).

Organotin Compounds. No definitive studies were located regarding absorption of organotin compounds in humans. The retention of tetralkyltin compounds in various tissues in rats provides qualitative evidence of absorption.

2.3.1.3 Dermal Exposure

Inorganic Tin Compounds. No studies were located regarding absorption in humans or animals after dermal exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding absorption in humans after dermal exposure to organotin compounds.

Renal tubular changes were observed in guinea pigs after dermal exposure up to 100 mg/kg/day bis(tributyltin)oxide for 50 days (Mori et al. 1984). The changes were similar to those seen with inorganic tin compounds after oral exposure and are suggestive of systemic absorption.

2.3.2 Distribution

Tin is widely distributed in human tissues. Table 2-5 shows the highest concentrations, which are located in the kidney, liver, lung and bone (Kehoe et al. 1940; Schroeder et al. 1964). Tin was not detected in brain tissue (Kehoe et al. 1940).

Studies have shown that tin accumulates in human tissues rapidly during the first ten years of life in kidney and liver (Schroeder et al. 1964). Kidney levels were not detected at birth and peaked (57-60 mg tin/kg) at l-10 years. Levels declined and remained constant after 11 years. Tin was not detected in the liver at birth but values of 48-60 mg tin/kg were found by age 10. In the lungs, tin appeared to increase with age, with the highest levels (53-64 mg tin/kg) at ages 51-84 (Schroeder et al. 1964). Although these data indicate trends in tin accumulation in human tissues, wide variations in tissue concentrations are known to occur. The variations are related to different exposure conditions.

2.3.2.1 Inhalation Exposure

Inorganic Tin Compounds. No studies were located regarding distribution in humans or animals after inhalation exposure to inorganic tin compounds.

Organotin Compounds. No studies were located regarding distribution in humans or animals after inhalation exposure to organotin compounds.

2.3.2.2 Oral Exposure

Inorganic Tin Compounds. No studies were 'located regarding distribution in humans after oral exposure to inorganic tin compounds.

Small amounts of tin from inorganic sources have been detected in the liver, kidney, and bone, with trace amounts in other tissues. Approximately 48 hours after oral administration of 20 mg tin/kg/day (as Sn [II] and Sn [IV] citrate) in rats, the percentages of the dosed Sn (II) or Sn (IV)/kg, respectively, detected in various tissue were 1.02 and 0.24 (skeleton), 0.08 and 0.02 (liver), and 0.09 and 0.02 (kidneys) (Hiles 1974). Differences in tissue concentrations of the two valence forms of tin suggest that tin is unlikely to be oxidized or reduced during absorption and systemic transport. In rats that received 20 mg tin/kg/day over 28 days, tin levels in kidneys and liver were approximately the same as after a single oral dose (Hiles 1974).

TABLE 2-5. Mean Tin Levels in Human Tissue[a]

Tissue	Wet weight (mg/kg)
Kidney	0.2-0.78
Heart	0.2
Brain	ND
Liver	0.35-1.0
Spleen	0.2
Lung	0.45-1.20
Muscle	0.1
Bone	0.5-8.0
Gastrointestinal tract	0.1-0.5

ND = not detected

[a]Adapted from Kehoe et al. 1940; Schroeder et al. 1964.

The half-life of Sn [II] for liver and kidney was reported to be 10-20 days. However, the levels in bone were eight times higher than those found after a single oral dose (Hiles 1974). A half-life of 20-40 days was reported for both Sn [II] and [IV] in bone of rats administered 20 mg Sn [II] or Sn [IV]/kg (Hiles 1974).

Other animal studies support the finding of low accumulation of tin in body tissues, including bone, liver, and kidneys. In rats orally administered 0.6, 2.0, and 6.0 mg tin/kg/day as stannous chloride for 13 weeks, tin levels in the liver and bone increased significantly ($p<0.0l$) over control values at the intermediate and highest dose tested, but not at 0.6 (Yamaguchi et al. 1980). The concentration of tin (in μg/g tissue) was 0.38 and 21.6 in the liver and bone (femur), respectively, following administration of 6 mg tin/kg/day. When 2.0 mg tin/kg/day was administered, tin level in bone was 7 μg tin/g ($p<0.01$). Corresponding levels in the control were 0.24 and 2.05. In rats fed 30.5 or 61.0 mg/kg/day stannous chloride for 105 weeks, concentrations of tin in the tissues were 9 (bone), 17 (kidney), and 0.2 μg/g (liver) (NTP 1982). Tin levels increased with higher doses. When females were fed comparable doses of stannous chloride, tin levels were higher than those detected in male tissues (NTP 1982). Concentrations (in μg tin/g wet tissue) were 20, 47, and 0.3 in bone, kidney, and liver, respectively. Tin levels increased at higher doses (NTP 1982). Mean concentrations in μg tin/g wet weight were 1.88 in spleen and lesser amounts (0.17-0.93) in kidney, liver, lung, and heart in rats administered 0.43 mg tin/kg/day throughout their lifetime as stannous chloride (Schroeder et al. 1968).

Tin has also been detected in blood and brain tissue after exposure to high dose levels. Blood tin increased in 1 week in rats that ingested tin in drinking water at a dose of 42.7 mg tin/kg/day as stannous chloride, but did not differ from control levels when rats were administered a dose of 8.5 mg tin/kg/day (Savolainen and Valkomen 1986). Tin has also been detected in brain tissue and levels increased with increased exposure duration. Brain tin accumulated at a dose of 42.7 mg tin/kg/day during an 18-week exposure period but did not increase during this same period at a dose of 8.5 mg tin/kg/day (Savolainen and Valkomen 1986).

Tin does not appear to readily cross the placenta. At 10 days of gestation, tin was not found in the uterine horns or combined fetuses and placentas in rats following daily ingestion of 20 mg tin/kg/day as $^{113}SnF_2$, or ^{113}SnF(Hiles 1974). However, at 21 days, fetuses of dams administered 20 mg/kg/day as SnF_2, contained very low levels of tin. The detection of low levels and the absence of developmental effects suggest placental restriction of tin transfer to the fetus.

Organotin compounds. No studies were located regarding distribution in humans after oral exposure to organotin compounds.

Tin has been detected in rats after oral administration of 10 mg/kg/day tetralkyltin compounds (tetraethyltin, tetrapropyltin, and tetrabutyltin) (Iwai et al. 1982b). The compounds were found in the gastrointestinal tract,

kidney and liver, while no retention was observed in brain and blood. The gastrointestinal tract retained primarily tetrapropyltin and tetrabutyltin. Levels (in μg tin/g wet tissue) were highest in the jejunum (5 and 4 μg tin/g, respectively). In the kidney, all 3 tetralkyltin compounds were found and levels ranged from 1 μg tin/g (tetrabutyltin) to less than 4 μg tin/g (tetraethyltin and tetrapropyltin). The liver retained primarily tetrabutyltin (approximately 2 μg tin/g). The authors' suggestion that the route, rate, and amount of excretion of the tetra- and trialkyltins depend on dialkylation, doses, physical and chemical properties, and route of administration appears reasonable.

Other studies involving trialkyltin compounds also show tin is retained in the liver; however, alkyl tin compounds are rapidly converted to metabolites. When rats were administered a single oral dose of 40 mg/kg tributyltin fluoride by gavage, there was a transient increase in tributyltin in the liver 24 hours after treatment (Iwai et al. 1981). However, a rapid decrease in hepatic tributyltin was observed after the initial increase and there was a corresponding increase in concentration of its metabolites (dibutyltin, monobutyltin, and inorganic Sn [IV] (Iwai et al. 1981). Similarly, tributyltin was detected in brain tissue in rats administered a single oral dose of 40 mg/kg tributyltin fluoride by gavage. More importantly, there appeared to be an increased accumulation of metabolites of tributyltin (monobutyltin and inorganic tin [IV]), suggesting dealkylation reactions in brain tissue (Iwai et al. 1981). These findings further suggest that the blood-brain barrier does not limit uptake of tin into the central nervous system.

The highest levels of tin were found in the liver and kidneys (15 mg/kg wet tissue) in rats administered 16 mg/kg/day bis(bis(tributyltin)oxide) (Krajnc et al. 1984). Levels in the brain and adipose tissue were l0%-20% of the kidney and liver' levels (Krajnc et al. 1984). These levels appear to be similar to the rat data reported by Iwai et al. (1981, 1982b).

2.3.2.3 Dermal Exposure

Inorganic Tin Compounds. No studies were located regarding distribution in humans or animals after dermal exposure to inorganic compounds.

Organotin Compounds. No studies were located regarding distribution in humans or animals after dermal exposure to organotin compounds.

2.3.3 Metabolism

Inorganic Tin Compounds. No studies were located in humans or animals on metabolism of inorganic tin after inhalation, oral, or dermal exposure.

Organotin Compounds. No studies were located in humans on metabolism after inhalation, oral, or dermal exposure to organotin compounds. However, it is suggested that the appearance of tin in urine may be used as evidence of metabolism of organotin compounds.

In animals, there are limited data on the metabolic conversion of tin compounds in vivo. A decrease in tributyltin and a moderate-to-large increase of metabolites in the liver of rats administered a single oral dose of 40 mg/kg tributyltin fluoride suggest dealkylation is a major reaction (Iwai et al. 1981). Studies involving metabolism of organotin compounds after parenteral exposure and in the in vitro tests support these findings. The mechanism of conversion is not clear; however, oxidative mechanisms may be involved. When rats were administered a single intravenous dose of 20 mg/kg tetraethyltin, triethyltin was detected in several tissues with highest concentration in the blood and liver (Cremer 1958). A high concentration of triethyltin was found in the liver of a rabbit that received a single intravenous injection of 25 mg/kg tetraethyltin (Cremer 1958). However, lower concentrations were detected in kidneys, brain, and whole blood. In the in vitro tests, liver slices converted tetraethyltin to triethyltin more rapidly than kidney slices; brain and blood samples did not convert tetraethyltin to triethyltin (Cremer 1958). The findings from both in vivo and in vitro studies indicate that the liver is the most active site of the conversion of tetraethyltin into triethyltin.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Inorganic Tin Compounds. No studies were located regarding excretion in humans or animals after inhalation exposure to inorganic tin.

Organotin Compounds. Limited excretion data from occupational studies suggest tin may be absorbed to some extent. Approximately 625-1,600 ppb were detected in urine samples of workers exposed for an unspecified duration (Rey et al. 1984). No data were provided on time of detection after exposure. Conditions in the plant were conducive to both inhalation and dermal exposures. Therefore, the extent to which absorption followed inhalation exposure in this study is inconclusive.

2.3.4.2 Oral Exposure

Inorganic Tin Compounds. No studies were located regarding excretion in humans after oral exposure to inorganic tin compounds.

Animal data suggest excretion is rapid in rats and occurs primarily in feces. At 48 hours after dosing, 95%-100% of the administered ^{113}Sn (as Sn [II] or Sn [IV] citrate, $Sn_2P_2O_7$ SnF_2, and SnF_4,) was recovered in feces while less than 1% was detected in urine (Hiles 1974). Of the label appearing in urine, 80%-90% of the radioactivity was detected in the first 10 hours after exposure, while no ^{113}Sn was detected in feces during this period.

Organotin Compounds. No studies were located regarding excretion in humans after oral exposure to organotin compounds.

2.3.4.3 Dermal Exposure

Inorganic Tin Compounds. No studies were located regarding excretion in humans or animals after dermal exposure to inorganic tin compounds,

Organotin Compounds. No studies were located regarding excretion in humans or animals after dermal exposure to organotin compounds.

2.4 RELEVANCE TO PUBLIC HEALTH

The data presented in Section 2.2 for acute-duration intermediate-duration and chronic-duration exposures to inorganic and organic tin are inadequate to establish MRL values by either the inhalation or oral routes of exposure. NOAEL and LOAEL values were identified for both inorganic and organic tin compounds but were determined to be unsuitable for use as the basis of MRL values. Effects of inorganic tin compounds on hematopoiesis, liver, kidney, and the gastrointestinal tract were noted in several studies of intermediate duration. However, the data were confounded by decreases in food intake, poor weight gain, and differences in the trace nutrient composition of the standard diets, In addition, the tin content of the standard diet was generally not known and the data on compounds other than stannous chloride was minimal. Accordingly, it was not possible to ascribe the observed effects solely to tin.

The data presented for organotins came from studies of a broad assortment of different chemicals with differing organic moieties. No one organic tin compound could be regarded as typical of the organotin family. This diversity in compound characterizations and effects contributed to the decision that valid MRL values could not be calculated for organotin compounds. Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for tin and its compounds due to the lack of an appropriate methodology for the development of dermal MRLs.

Dermal contact with or ingestion of soil or sediments contaminated with tin or its compounds could be possible routes of exposure for people living near hazardous waste sites. Contaminated drinking water should not be regarded as an important route because tin compounds are generally not very water soluble. Stannous chloride is an exception. Likewise, tin compounds are not volatile, and inhalation exposure should not usually be a problem around waste sites. Ingestion of food or beverages from tin cans and occupational exposure appear to be the major potential sources of health concerns.

There is essentially no information concerning effects in humans or animals after inhalation of inorganic tin compounds except for deposits of tin observed in the lungs of workers exposed for a long time. No functional changes or systemic disease were observed and this finding has not been noted in animals.

By contrast, organotin compounds produce similar health effects in humans and animals after acute and intermediate inhalation exposure. Deaths in workers exposed to methyltins were preceded by respiratory depression and neurobehavioral changes. Autopsies revealed liver and kidney pathology. Irritation of the upper respiratory tract and skin and eye irritation have been seen in humans. Generally speaking, the animal data confirm the human effects after inhalation exposure to the organotins.

The potential effects of oral exposure to both inorganic tin and organotin compounds have been identified in numerous animal studies. Direct observations in humans are few and no epidemiological studies were located. Gastroenteritis was described for people who ate food or drank juice from tin cans processed before lacquering and other newer technology was developed. A large number of deaths, preceded by neurobehavioral disturbances, occurred in people after they had taken the drug, Stalinon, which contained a triethyltin compound. The neurotoxic effects of triethyltin and trimethyltin compounds have been demonstrated in animal studies of acute and intermediate duration.

Effects noted in animals after oral exposure to inorganic tin compounds are much less pronounced than for the organotins but do include observations of gastrointestinal disturbances, anemia, liver, and kidney changes. Organotin compounds produce similar changes plus immunological, neurological, and some developmental and reproductive effects.

Although dermal exposure is potentially important as a route of exposure around hazardous waste sites, the limited data on dermal/ocular toxicity do not permit a complete evaluation of the toxic potential of the tin compounds by this route. Skin and eye irritation and dermatitis have been observed in both humans and animals after acute and intermediate exposure to inorganic tin or organotin compounds. None of the compounds appear to cause dermal sensitization in humans or animals.

No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to inorganic or organotin compounds.

There is also no conclusive evidence that inorganic tin compounds have carcinogenic properties. However, there are data which indicate that organotin compounds (bis(tributyltin)oxide and triphenyltin hydroxide) may be tumorigenic at low levels of tin. Bis(tributyltin)oxide (2.5 mg/kg/day) and triphenyl tin hydroxide (0.3-6.2 mg/kg/day) were associated with pituitary adenomas in rats of both sexes with exposures of 104-106 weeks. When triphenyltin hydroxide was administered, the pituitary adenomas were present only in the females and contributed to decreased longevity.

In the studies of long-term exposure of rats to both triphenyltin hydroxide and bis(tributyltin)oxide, most of the tumors were found in endocrine glands. In addition to the pituitary adenomas associated with bis(tributyltin)oxide and triphenyltin hydroxide, there was also an increased incidence of pheochromocytomas of the adrenal gland, parathyroid carcinomas

and pancreatic adenocarcinomas in animals from at least one sex. Triphenyltin hydroxide was associated with an increased incidence of testicular Leydig cell tumors in male rats at the highest dose. Hepatic tumors were found in male and female mice following 80 weeks of triphenyltin hydroxide administration.

The EPA Office of Pesticide Programs reviewed the data for the tumorigenicity of triphenyltin hydroxide and classified it as a possible human carcinogen (Group B2) based on the tumors found in both rats and mice during chronic studies of carcinogenicity: The most appropriate estimate of the unit risk in human equivalents was a ql* of 2.8 $(mg/kg/day)^{-1}$ from the data on pituitary gland adenomas in female rats.

Death. No deaths in humans have been reported after either oral or dermal exposure to inorganic tin compounds or following dermal exposure to organotin compounds. Deaths have occurred in humans and animals after inhalation and oral exposures of organotin compounds. Triethyltins have specifically been implicated in deaths of people occupationally exposed and those taking an oral drug containing a triethyltin compound. Neurobehavioral changes were seen prior to death and in survivors. For some individuals the neurological problems were resolved within 6 months. For others, symptoms persisted and required medical treatment for over 2 years. Animal studies have confirmed these signs. Inorganic tin and organotin levels at hazardous waste sites would probably not be high enough to result in deaths of humans. However, the long term exposure of humans to low levels of tin compounds at waste sites, in industrial neighborhoods, or in the environment has not been evaluated in terms of effects on human longevity.

Systemic Effects.

Respiratory Effects. Respiratory effects were seen only after inhalation exposure of humans to inorganic tin and organotin compounds and animals to inorganic tin compounds. Methyltins caused respiratory depression prior to death of workers occupationally exposed. A benign form of pneumoconiosis, known as stannosis, was observed in workers exposed to stannic oxide dust and fumes for 15-20 years. However, no functional impairment or systemic disease was seen. Irritation of the upper respiratory tract has also been described in workers using bis(tributyltin)oxide. No such effects were seen in humans or animals after oral or dermal exposure to these compounds. There exists the possibility of adverse respiratory effects resulting from inhaling tin compound fumes and dust over a period of time at hazardous waste sites but probably only in very rare instances.

Gastrointestinal Effects. Gastrointestinal effects of different severities, consisting of irritation of the mucous membranes of the stomach and intestines, have been observed in humans. This has usually been after oral exposure to inorganic tin via the eating of food or drinking liquids from tin containers. Animals have exhibited distention of the stomach and intestines after oral exposure to both inorganic tin and organotin compounds. No such effects have been observed in humans or animals after inhalation or dermal exposure. Ingestion of tin-contaminated soils or sediments at

hazardous waste sites could present gastrointestinal problems but probably only in rare instances.

Hematological Effects. No hematological effects have been observed in humans after inhalation, oral, or dermal exposure. Anemia was seen in rats exposed to repeated oral doses of both inorganic tin and organotin compounds. No such effects were observed in rats after inhalation or dermal exposure. It is unlikely that tin compounds would cause hematological effects in people in the vicinity of hazardous waste sites.

Hepatic Effects. Hepatic effects have been observed following oral exposure of rats to inorganic tin as stannous chloride. However, the observed effects (bile duct hyperplasia, fat infiltration, and cytoplasmic clarity) were not present in the NTP subchronic, and chronic investigations of this compound in rats and mice even at higher doses. There are reports of liver pathology, consisting primarily of fatty degeneration, for humans and animals exposed by inhalation and for animals after oral exposures to organotin compounds. This change occurs after short-term exposures. It appears that major systemic effects of the organotins, as seen in animals after exposure in acute- and intermediate-duration studies, are inflammation, necrosis, and sometimes hyperplasia of the bile duct with necrosis in the liver. Although these changes have not been reported in humans, the consistency and severity of the effects in several animal species must allow for the possibility of these effects in humans after exposure to both inorganic tin and organotins.

Renal Effects. Some changes in renal histopathology were seen in several short to intermediate-duration studies of stannous chloride. However, these affects were not present in either rats or mice during the NTP investigations of this compound. The absence of renal calcareous deposits in females and protein droplets in males exposed to high doses of stannous chloride despite their presence in the controls and at low doses cannot be clearly categorized as an adverse effect.

Proximal tubule epithelial degeneration is the major renal change observed in humans after inhalation exposure to organotin compounds. Similar changes have been observed in animals following inhalation, oral, and dermal exposure to organotins. As with the hepatic changes, the possibility that tin compounds may cause renal effects at hazardous waste sites must be considered.

Dermal/Ocular Effects. Skin and eye irritations and dermatitis, but not sensitization, have been reported in humans and animals after dermal exposure of acute and intermediate-duration to both inorganic tin and organotin compounds. Mice also experienced a dermatological reaction to triphenyltin hydroxide after oral exposure over a period of 80 weeks. There is a reasonable probability of some skin, eye, and other mucous membrane contact with compounds at hazardous waste sites and the likelihood of irritation and other effects occurring.

Immunological Effects. No studies were located regarding immunological effects in humans after inhalation, oral, or dermal exposure to inorganic tin or organotin compounds. Such studies are also lacking for animals exposed to inorganic tin compounds. However, there are a number of studies that report immunological effects in animals after oral exposure to organotins. The rat is the most sensitive species based on intermediate-duration studies of 4-13 weeks. The major systemic effects are decreased weights of the thymus and lymph nodes. Serum immunoglobin concentrations were also decreased in mice and rats exposed to tin as triphenyltin hydroxide for 26-80 weeks. Comparative studies indicate that the pre-weanling rat is more sensitive than the adult rat. The lack of data from human studies makes it difficult to predict impairment of the immune system in persons at hazardous waste sites. The consistent animal findings should make this an area of potential concern.

Neurological Effects. Studies have been reported for humans after inhalation and oral exposure to organotin compounds and oral exposure to inorganic tin compounds. No human studies for dermal exposure to the compounds have been located. Animal studies are limited to data obtained after oral exposure to either inorganic tin or organotin compounds. In some individuals neurological problems persisted and required medical attention even 2 years after exposure.

Neurobehavioral symptoms developed by chemical workers after exposure to methyltins included impaired memory, disorientation, aggressiveness, psychotic behavior, syncope, and loss of consciousness. Some of the symptoms persisted and memory loss was apparent for 6 months in workers able to return to work.

In the persons that received the drug, Stalinon, and died, symptoms prior to death included vertigo, intense headache, photophobia, altered consciousness, visual impairment, convulsions, and sensory disturbances. Autopsies revealed edema in the white matter of the central nervous system.

In acute- and intermediate-duration animal studies, signs of toxicity and pathology changes, characteristic of the trimethyltin and triethyltin compounds, were reported. The animal data also confirm the human effects described.

The human information is based largely on case reports not epidemiology studies. Chemicals other than organotins were always involved. Exposure levels and durations were not well documented in the human reports and exaggerated doses were used on the animal studies. Despite the uncertainties, neurobehavioral changes must be looked for in persons involved with accidental spills of tin compounds, in industrial settings, or at hazardous waste sites.

Developmental Effects. Except for two limited oral studies of organotin compounds, no other studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to inorganic tin or organotin compounds. Bis(tributyltin)oxide produced a dose-related decrease in fetal weights, increase of cleft palates, and other abnormalities. The relevance of these data to humans is not known.

Reproductive Effects. The two studies of developmental effects (see Developmental Effects) included observations of maternal toxicity, maternal deficits in weight gain were present in mice and rats and mice exhibited an increased rate of resorptions. Maternal toxicity undoubtedly was the most important contributing factor in producing the developmental effects. The relevance of the findings to humans is not clear.

No other studies were located regarding reproductive effects in humans or animals after inhalation, oral, or dermal exposure to inorganic tin or organotin compounds.

Genotoxic Effects. No studies were located regarding genotoxic effects after inhalation, oral, or dermal exposure to inorganic tin or organotin compounds. There are limited in vitro data on inorganic tin compounds which show mixed results (Table 2-6). DNA damage was noted with mammalian cells treated with stannous chloride (McLean et al. 1983). Cytogenetic studies also gave positive responses with stannous chloride for chromosomal aberrations and sister chromatid exchanges (Gulati et al. 1989). Stannous chloride has also been reported to rapidly convert hydroperoxy thymidine to mutagenic hydroxymethyl deoxyuridine species in vitro (Tofigh and Frenkel 1987). This may be indicative of a redox component in the genotoxic potential of stannous chloride in vivo. However, the relevance of this finding to human health effects is unclear. No in vivo data were located for inorganic tin compounds.

As shown in Tables 2-7 and 2-8, there are both in vitro and in vivo genotoxicity data for organotin compounds, particularly bis(tributyltin)oxide. The results from most in vitro studies were negative. However, base-pair substitutions were produced in an activated Salmonella typhimurium fluctuation test of bis(tributyltin)oxide (Davis et al. 1987). In addition, bis(tributyltin)oxide produced chromosomal aberrations in hamster ovary cells with activation (Davis et al. 1987). In vivo micronucleus tests of bis(tributyltin)oxide in mice produced mixed results (Table 2-8). The relevance of the genotoxic data to humans is not clear.

Cancer. No epidemiology studies or case reports for humans were located regarding cancer effects after inhalation, oral, or dermal exposure to inorganic or organotin compounds. Several animal bioassays have been conducted in rats and mice. These have been essentially negative results with respect to predicting carcinogenic potential of inorganic tin compounds (e.g., stannous chloride). The increased incidences of benign and other tumors observed with organotins leaves the question of their carcinogenicity unanswered at this time. The relevance of such findings to humans in not clear.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

TABLE 2-6. Genotoxicity of Inorganic Tin Compounds In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Bacillus subtilis	Rec-assay	No data	-	Nishioka 1975	Stannous chloride
B. subtilis	Rec-assay	No data	-	Nishioka 1975	Stannic oxide
Mammalian cells:					
Chinese hamster ovary cells	DNA damage: Alkaline sucrose gradient analysis	No data	+	McLean et al. 1983	Stannous chloride
Chinese hamster ovary cells	DNA damage: Alkaline sucrose gradient analysis	No data	-	McLean et al. 1983	Stannic chloride
Chinese hamster ovary cells	Sister chromatid exchanges	+	+	Gulati et al. 1989	Stannous chloride
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Gulati et al. 1989	Stannous chloride

+ = positive result; - = negative result; DNA = deoxyribonucleic acid

TABLE 2-7. Genotoxicity of Organotin Compounds In Vitro

Species (test system)	End point	Results[a] With activation	Results[a] Without activation	Reference
Prokaryotic organisms:				
Bacillus subtilis	Rec-assay	No data	-	Davis et al. 1987
K. pneumonas	Fluctuation test	No data	-	Davis et al. 1987
Salmonella typhimurium	Plate assay	-	-	Davis et al. 1987
S. typhimurium	Hepatocyte	-	No data	Davis et al. 1987
S. typhimurium	Mediated assay	-	No data	Davis et al. 1987
S. typhimurium	Fluctuation test	+	-	Davis et al. 1987
Eukaryotic organisms:				
Saccharomayces pombe	Forward mutation	-	-	Davis et al. 1987
Saccharomyces cerevesiae	Mitotic gene conversion	-	-	Davis et al. 1987
Mammalian cells:				
Chinese hamster cells	8-Azaguanine and ovarian resistance	-	-	Davis et al. 1987
Chinese hamster cells	6-Thioguanine resistance	-	-	Davis et al. 1987
Mouse lymphoma cells	6-Thioguanine and Buer resistance	No data	-	Davis et al. 1987
Chinese hamster cells	Sister chromatid exchange	-	-	Davis et al. 1987
Chinese hamster cells	Chromosomal aberrations	+	-	Davis et al. 1987
Chinese hamster cells	Inhibition of metabolic cooperation	No data	-	Davis et al. 1987

[a]All information is presented for bis(tributyltin)oxide.

+ = positive result; - = negative result

TABLE 2-8. Genotoxicity of Organotin Compounds In Vivo

Species (test system)	End point	Results[a]	Reference
Insect system:			
Drosophila melanogaster	Test for sex-linked recessive lethal mutations	- (after feeding) - (after injection)	Davis et al. 1987
Mammalian systems:			
Mice	Micronucleus test; single dose 60 mg/kg body weight	+ (increased micronuclei in erythrocytes)	Davis et al. 1987
Mice	Micronucleus test; cytotoxic doses; highest 125 mg/kg body weight	- (no evidence of chromosomal damage or malfunction)	Schweinfurth and Gunzel 1987

[a]All information is presented for bis(tributyltin)oxide.

+ = positive result; - = negative result

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to inorganic tin and organotin compounds are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by inorganic tin and organotin compounds are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Inorganic Tin and Organotin Compounds

Inorganic tin compounds are generally poorly absorbed (l-3%) and are rapidly excreted in the feces. The half-life for inorganic tin in the major tissues range from 10 to 40 days. Except for potential oral exposure due to eating foods from tin containers and using toothpastes containing stannous fluoride, humans are not expected to be exposed to inorganic tin compounds in any regular way. Inorganic tin has been found in low concentrations in virtually all human tissues, in feces, in the urine, and in the blood. The amounts vary greatly from organ to organ. Because inorganic tin compounds

exhibit a low order of toxicity in humans and animals and exposure data by the inhalation, oral, and dermal routes are limited, primary biomarkers for these compounds cannot be identified at this time. The tin levels measured in animal tissues, feces, urine, and blood do not provide sufficient information to identify the magnitude, timing, or duration of exposure.

Some organotin compounds such as the triethyltins and trimethyltins, are fairly well absorbed. This is based on health effects observed, particularly after oral exposures. Some tentative biomarkers, albeit not specific, are discussed in Section 2.5.2.

2.5.2 Biomarkers Used to Characterize Effects Caused by Inorganic Tin and Organotin Compounds

As mentioned above, there are no definitive biomarkers of exposure for the inorganic tin compounds. This is also true in attempting to characterize effects since the data in humans and animals have not identified any tininduced physiological change which can be used to document adverse effects from tin exposure.

Organotin compounds do produce more specific effects than inorganic tin compounds and there are sensitive organs and systems. The data are largely derived from acute and intermediate-duration studies in animals. There are reports of effects on the bile duct and liver, immune system (thymus and lymphoid organs), nervous system (pathological and functional changes), kidneys, and blood. Most of the effects are not specific only to organotin compounds but the effects are consistent enough to tentatively identify biomarkers that could be used. These would include complete hematology, including differential leucocyte counts; blood chemistry, including alkaline phosphatase and serum transaminase; urinalysis; and neurobehavioral tests.

Since inorganic tin and organotin compounds are not associated with specific changes to biomolecules, pertibations of enzyme activities, or unique alterations of tissue pathology, there are no suitable biomarkers for effects from exposure to either inorganic or organic tin compounds.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Some studies describe interactions of inorganic tin and organotin compounds with other chemicals which either increase or decrease the toxicological properties of the tin compounds. Iron and copper lessen the effects of growth depression and decreased hemoglobin seen in rats fed stannous chloride at high doses for 4-13 weeks (DeGroot 1973). Tin also interacts with other essential metals. In bioavailability studies in humans, zinc uptake was decreased when tin, iron, and zinc were administered in equal doses (Solomon et al. 1983).

Sulfur-containing compounds have been shown *in vitro* to interact with tributyltin compounds to produce other compounds with lower hemolytic activity (Byington et al. 1974). It has also been shown *in vitro* that the toxic

properties of dibutyltin dichloride may be enhanced by meso,2-3,-dimercaptosuccinic acid, by means of a hydrophobic reaction with glutathione enzymes (Henninghausen and Merkord 1985). Such interactions could be of importance in treatment of organotin poisonings.

2.7 POPULATIONS THAT ABE UNUSUALLY SUSCEPTIBLE

There are no specific populations that have been identified that are unusually susceptible to either inorganic tin or organotin compounds with respect to health effects. However, based on the target organ and system effects seen with organotin compounds in animals, persons with liver disease, blood disorders, deficiencies of the immune system, neurobehavioral disorders, and perhaps kidney disease could be predisposed to adverse health effects of the compounds under appropriate conditions of exposure.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tin. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tin. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to tin may occur by inhalation, ingestion or dermal contact (see Chapter 5). Gastrointestinal effects have been observed following ingestion of inorganic tin compounds and ingestion or inhalation of organotin compounds may cause neurological effects (see Section 2.2). Inorganic tin salts are reported to be skin and eye irritants (WHO 1980).

The procedures used to reduce absorption following exposure to tin compounds include the following. Dermal/ocular exposure to tin compounds is treated by washing thoroughly with soap and water and flushing the eyes with water (Bronstein and Currance 1988). Water is administered for dilution following ingestion of tin compounds (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Studies in humans and animals indicate that tin can be retained by tissues (kidney, liver, lung, and bone) following exposure (Hiles 1974; Schroeder et al. 1964, 1968). However, since animal studies indicate that most of an administered dose of tin is excreted within 48 hours (Hiles 1974), it seems unlikely that efforts to enhance the elimination of tin would be of much benefit. Neither administration of D-penicillamine to increase urinary tin excretion nor chelation therapy with dimercaprol (BAL) seem to be effective in removing tin from the body (Ellenhorn and Barceloux 1988). It has been suggested the mechanism of action for tin in producing adverse health effects involves the inhibition of the hydrolysis of adenosine triphosphate (ATP) and uncoupling of oxidative phosphorylation in mitochrondia (WHO 1980). Currently, there are no methods for interfering with the mechanism of action of tin. However, as discussed above, iron and copper act to diminish the effects of tin on growth and hemoglobin levels (Degroot 1973). Similarly, sulfur-containing compounds diminished the hemolytic action of tributyltin

compounds (Byrington et al. 1974). These observations may be important in developing methods for interfering with the mechanism of action of tin, however further investigation is needed.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of inorganic tin and organotin compounds are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of inorganic tin or organotin compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Inorganic Tin and Organotin Compounds

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic tin or organotin compounds are summarized in Figures 2-4 and 2-5, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of inorganic tin or organotin compounds. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

Figure 2-4 provides the information for inorganic tin compounds. There are case reports that describe acute and chronic effects of inhaled inorganic tin compounds on humans. There are also reports of humans that developed health effects after oral exposure to food and drink from tin cans. Otherwise, no other studies were located regarding health effects in humans after inhalation, oral, or dermal routes of exposure.

The health effects of inorganic tin compounds have been chiefly studied in animals after oral exposure, as shown in Figure 2-4. The figure also shows that no inhalation studies and only a few dermal studies were located regarding health effects from inorganic tin compounds.

FIGURE 2-4. Existing Information on Health Effects of Inorganic Tin Compounds

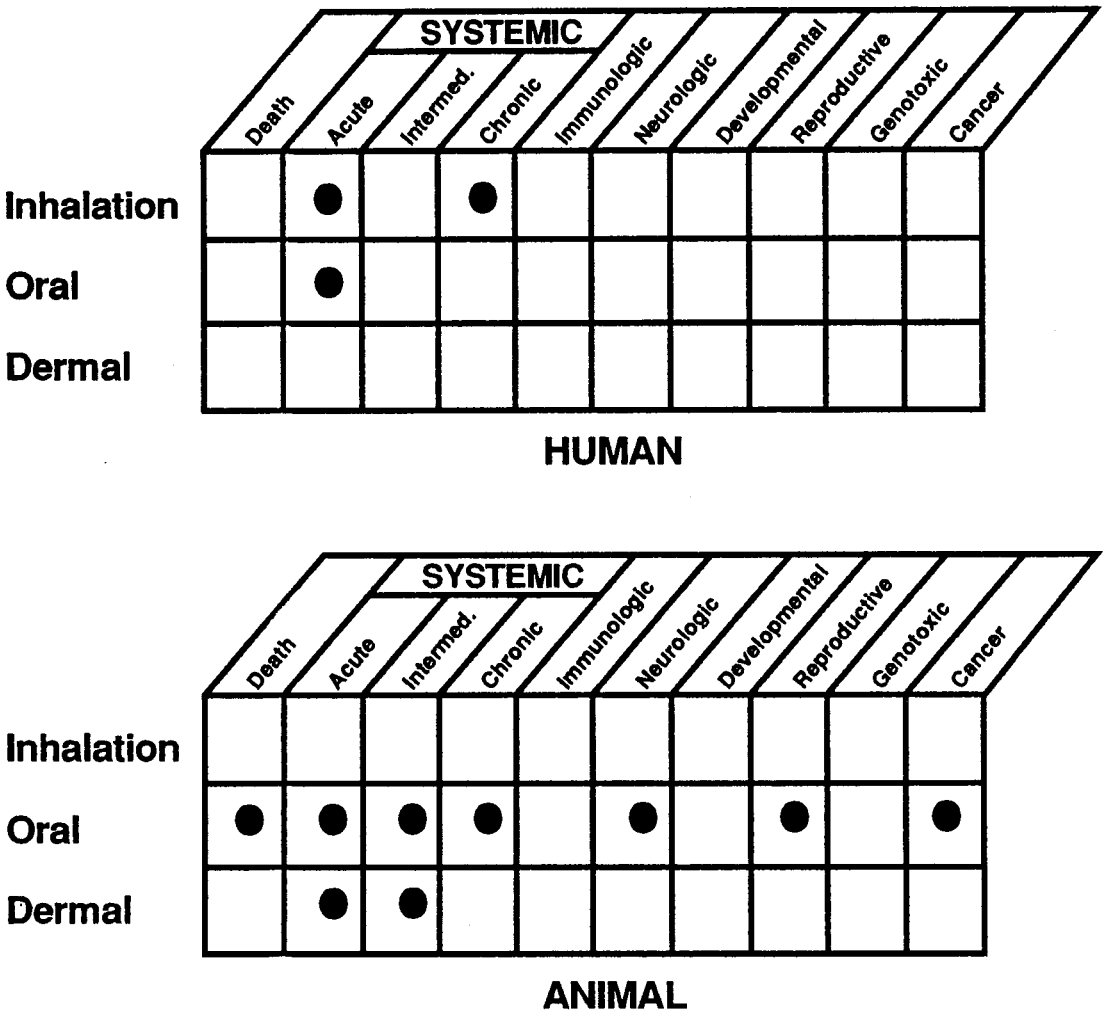
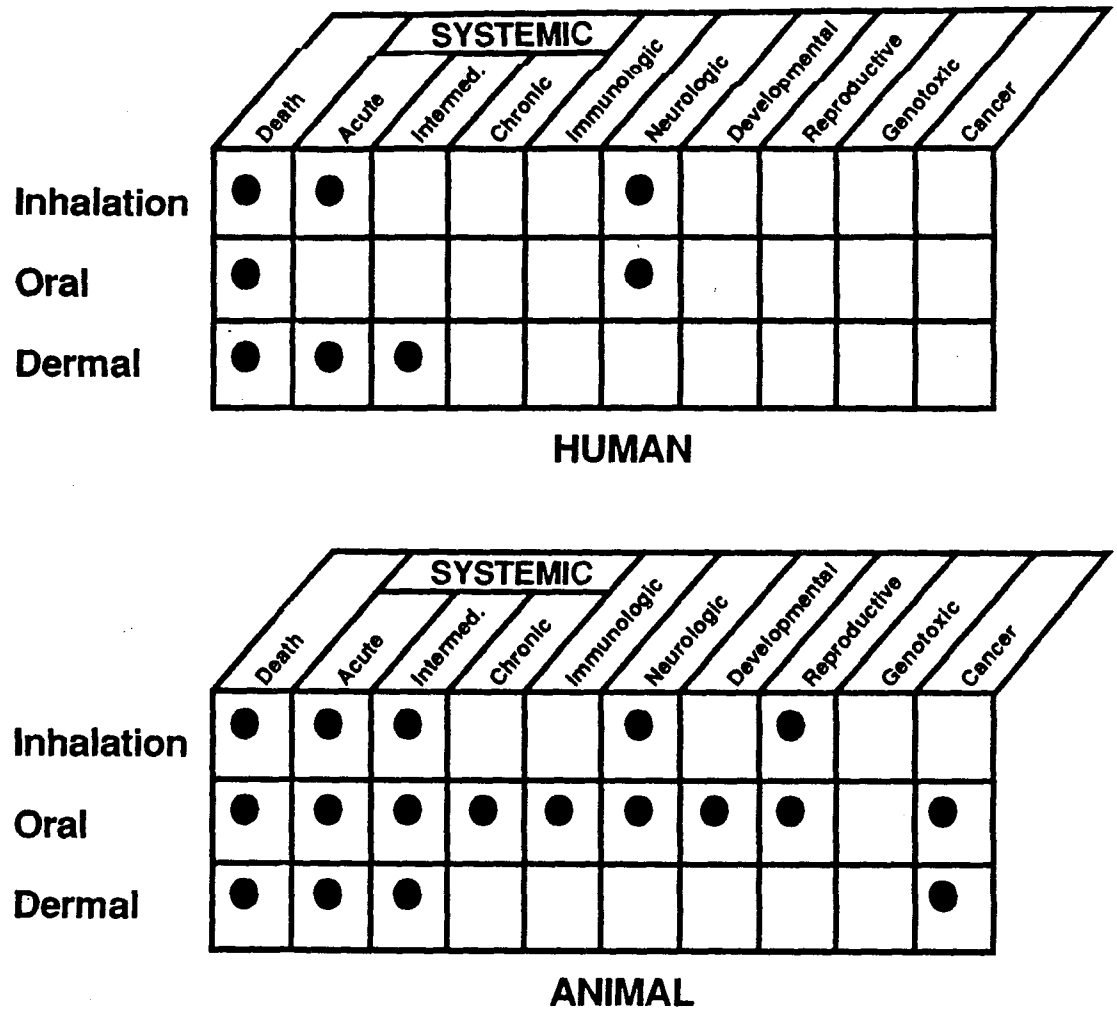


FIGURE 2-5. Existing Information on Health Effects of Organotin Compounds



● Existing Studies

Figure 2-5 provides health effects information on humans and animals after exposure to organotin compounds. The database for these compounds is much more complete than for the inorganic tin compounds. There are case reports that describe deaths and other effects associated with inhalation, oral, and, secondarily, dermal routes of exposure. In addition to acuteduration inhalation studies and acute and intermediate dermal studies, there are reports of neurobehavioral effects in humans after inhalation and oral exposures.

The extent of the database on health effects in animals resulting from exposure to organotin compounds is clearly shown in Figure 2-5. Except for genotoxic studies, there are oral studies that describe all the other toxicological end points considered in this profile. By contrast, the information is more limited for the inhalation and dermal routes of exposure.

2.9.2 Data Needs

Informational needs are discussed in light of the current data that exist for both inorganic tin and organotin compounds and how additional information will help in assessing potential toxicity or human health effects after inhalation, oral, and dermal exposures.

Acute-Duration Exposure. No target organs can be identified in humans or animals after acute inhalation, oral, or dermal exposure to inorganic tin compounds. Data were insufficient to derive inhalation or oral MRLs due to this lack of target organs and also the lack of exposure level information. However, even with sufficient data, the number of inorganic tin compound structures would not permit an appropriate selection of a typical compound as a representative of the entire class. Oral absorption and other toxicokinetic data suggest that inorganic tin compounds are not readily absorbed (less than 5%) (Hiles 1974). As a result, there are few data regarding acute effects of these compounds. There does exist the possibility for brief human exposures to inorganic tin compounds by eating food or drinking liquids from tin cans, in the workplace, at accidental spill sites, and at hazardous waste sites. However, considering the poor absorption by the oral route, the lack of effects after inhalation exposure, and only limited effects of dermal exposure, development of additional acute data would not be particularly useful.

Target organ toxicity is suggested for humans after acute inhalation exposure of organotin compounds, Deaths occurred after workplace exposures and symptomatology preceding death included respiratory depression in one case and renal failure in another (NIOSH 1976; Rey et al. 1984). Animal studies did not provide confirmatory data. Because of limitations in human data and few appropriate NOAEL and LOAEL values in animals, an MRL for acute inhalation exposure has not been determined. However, even with sufficient data the large number of organotin compounds would not permit an appropriate selection of a typical compound as a representative of the entire class. By contrast, some target organs have been identified in both humans and animals after acute oral exposures. A large number of people died after receiving an oral

medication containing organotin compounds (WHO 1980). Neurotoxic effects were observed preceding death and are discussed in the appropriate section below. Animals exposed orally to organotin compounds have demonstrated liver/bile duct and kidney toxicity in acute-duration studies. Toxicokinetics data provide additional data since some organotins are retained in the liver and kidneys after oral exposures (Krajnc et al. 1984). Although there are NOAEL and LOAEL values for liver and kidney effects in animals, the data are insufficient to determine an appropriate MRL for acute oral exposure. However, even with sufficient data, the large number of organotin compounds would not permit an appropriate selection of a typical compound as representative of the entire class. There does exist the possibility for brief human exposures to organotin compounds in the workplace, at accidental spill sites, and at hazardous waste sites. Some organotin compounds are absorbed after oral exposure and others may produce dermal and ocular effects. Development of a range of threshold exposure concentrations by these routes would be useful in determining the lowest doses that could produce the acute health effects in brief exposure situations.

Intermediate-Duration Exposure. There are currently no data concerning the effects of inorganic tin or organotin compounds on humans for this exposure duration for the inhalation, oral, or dermal routes of exposure.

Based on animal studies of inorganic tin compounds in rodents, primarily rats and mice, by the oral route of exposure, the target organs and systems identified were the gastrointestinal tract, the blood, the kidney, the liver, and bile ducts (DeGroot et al. 1973; Dreef-van der Meulen 1974; Janssen et al. 1985; NTP 1982; Schroeder et al. 1968). The blood and liver/bile duct effects were also observed with organotin compounds after intermediate oral exposures (Barnes and Magee 1958; Jang et al. 1986; Krajnc et al. 1984; Wester et al. 1987). Decreased body weight gains and reduced food intake were consistent findings for both inorganic tin and organotin compounds after oral exposures of intermediate duration (DeGroot et al. 1973; Dreef-van der Meulen 1974; Elsea and Paynter 1958; Janssen et al. 1985; Krajnc et al. 1984). Future research efforts should utilize a pair-fed control protocol. In addition, investigations of oral exposures to inorganic tin compounds should employ diets with adequate and balanced levels of trace minerals and known tin content. Specific target organs could not be identified for inorganic tin or organotin compounds exposed by the inhalation and dermal routes for this exposure duration. Toxicokinetic studies tend to support the results of the intermediate-duration toxicity studies as was the case for the acute-duration studies.

Although there are NOAEL and LOAEL values for both inorganic and organic tin compounds which pertain to the effects listed above in animals, the data are not sufficient to determine an appropriate MRL for intermediate oral exposure. However, even with sufficient data, the number of organotin compounds would not permit an appropriate selection of a typical compound as a representative of the entire class. There does exist the possibility for repeated human exposures to both inorganic tin and organotin compounds in the workplace, at accidental spill sites, and at hazardous waste sites. There may

be the possibility of eating contaminated food or drinking juices and other liquids that carry residues of inorganic tin compounds. Considering the specific oral data in animals and the general lack of effects after inhalation or dermal routes of exposure, further studies of intermediate duration (e.g., 90 day studies) would be useful for both inorganic tin and organotin compounds. The purpose of such studies would be to quantify some of the earlier qualitative observations and to expand the end points used to evaluate and characterize the toxic effects. A range of threshold concentrations producing health effects after repeated exposures by different routes could be determined. For organotin compounds, data which would allow for evaluation of the effects of the organic moiety on toxicity would be helpful.

Chronic-Duration Exposure and Cancer. No target organs have been identified in humans or animals after chronic inhalation exposure to inorganic tin or organotin compounds. One possible target organ is the lung. Tin deposits were observed in chest x-rays of workers exposed to stannic oxide fumes for 15-20 years. However, there was no impairment of pulmonary function or systemic disease. This observation was later reported in a large number of tin foundry workers. However, no retrospective or prospective epidemiological studies have been performed. No target organs have been identified in humans after chronic oral exposure to inorganic tin or organotin compounds. Chronic animal studies, using life-time feeding in rats and mice, did not report consistent effects that could be used to identify target organs of toxicity. The tumorigenic responses that were suggested by the available studies are discussed below. In a chronic bioassay of stannous chloride in rats, there were no nonneoplastic effects that appeared to be due to the feeding of the compound (NTP 1982). The changes seen in the gastrointestinal tract at doses of 115.9 mg/kg/day in rats and 301.3 mg/kg/day in mice with intermediate-duration studies were not confirmed in the chronic study using lower exposure levels (3.5 and 61 mg/kg/day in rats and 79.3 and 158.6 mg/kg/day in mice). Similarly, organotin compounds fed on a chronic basis did not produce the changes observed with intermediate-duration except for some reduced survival hepatic effects and body weight gains. A preliminary report of a chronic oral study of bis(tributyltin)oxide described some immunological and endocrine changes (Krajnc et al. 1984; Tennekes et al. 1989a, 1989b; Wester et al. 1987). There are no data regarding adverse health effects in humans or animals after chronic dermal exposure to inorganic tin or organotin compounds. Since chronic NOAEL and LOAEL values in animals are limited, an appropriate MRL for chronic inhalation or oral exposure could not be determined. However, even with sufficient data, the number of inorganic tin and organotin compounds would not permit appropriate selection of typical compounds as representatives of each class.

There is currently no information from case reports on epidemiological studies which report on the carcinogenic potential of inorganic tin or organotin compounds after inhalation, oral, or dermal exposures in humans. Likewise, such data are lacking for inhalation and dermal studies of inorganic tin and organotin compounds in animals. Oral bioassays in animals have been conducted for stannous chloride, dibutyltin diacetate, triphenyltin hydroxide, and bis(tributyltin)oxide. Based on the available data, inorganic tin

compounds do not appear to be tumorigenic. There are indications, however, that some of the organic tin compounds may be carcinogenic. The EPA Office of Pesticide Programs has assigned a B2 possible human carcinogen designation for triphenyltin hydroxide based on pituitary adenomas found in female rats administered this compound over a lifetime (Tennekes et al. 1989a). Triphenyltin hydroxide was also associated with an increased incidence of testicular tumors in male rats and hepatic adenomas and carcinomas in male and female mice (Tennekes et al. 1989a, 1989b). Tumors were associated with the feeding of other organotin compounds, but, could not clearly be associated with the feeding of the compound. These tumors included hepatocellular adenomas and possible carcinomas of rats fed dibutyltin diacetate, and benign pituitary, adrenal, parathyroid, and pancreatic tumors in bis(tributyltin) oxide-fed rats. There was also the suggestion of uterine neoplasms in rats fed dibutyltin diacetate but the evaluation was compromised by the loss of tissues (NC1 1978b).

Toxicokinetic data are too limited to help explain the action of either the compounds fed in the bioassay studies or potential breakdown products formed during metabolism, which might have contributed to the production of the tumors observed. Knowledge concerning the fates of the organic and tin moieties from these compounds and the contribution of each moiety to the mechanism for carcinogenesis are needed in order to evaluate the role of tin in the tumorigenic response. Case studies and retrospective or prospective epidemiological studies of humans chronically exposed to low levels of inorganic tin or organotin compounds by all routes would be helpful in assessing carcinogenic potential in industrial neighborhoods, at hazardous waste sites, and in occupational settings.

Genotoxicity. There are no human data regarding the genotoxic potential of inorganic tin or organotin compounds after inhalation, oral, or dermal exposures. The limited in vitro data on inorganic tin compounds show mixed results. Most of the in vitro studies of organotin compounds produced negative results. However, common to both classes of compounds was the in vitro production of chromosomal aberrations (Davis et al. 1987; Gulati et al. 1989). Similar in vivo cytogenetic studies of exposed humans or animals would be useful. The genotoxic changes reported for inorganic and organic tin compounds are suggestive of carcinogenic potential, particularly in light of the negative carcinogenicity study results in animals.

Reproductive Toxicity. There are currently limited data available regarding the reproductive toxicity of inorganic tin or organotin compounds after inhalation, oral, or dermal exposures in either humans or animals. The limited toxicokinetic data indicate that inorganic tin is poorly absorbed and that selected organotin compounds such as trimethyl- and triethyltins appear to be absorbed slightly better. Inorganic tin does not appear to readily cross the placenta (Hiles 1974). There is a report of moderate testicular degeneration for rats exposed orally to high doses of stannous chloride (DeGroot et al. 1973). However, no

reproductive effects were observed in animals after inhalation or dermal exposure to inorganic tin compounds.

Organotin compounds have produced reproductive effects in animals after both inhalation and oral exposures. Pregnancy rates were reduced in rats that inhaled tributyltin bromide but partial reversibility was also observed when the compound was discontinued (Iwamoto 1960). Oral feeding of bis(tributyltin)oxide to mice produced maternal toxicity with increased resorptions and developmental effects (Davis et al. 1987). Maternal toxicity also occurred in rats given triphenyltin hydroxide; testicular atrophy and Leydig cell hyperplasia occurred in males exposed to this same compound (Tennekes et al. 1989a). Since there is the suggestion that the reproductive system could be a target organ and it is desirable to have such data for the inhalation and oral routes prior to deriving MRLs, specific reproductive organ pathology should be included in the 90 day studies. Multigeneration studies would be useful in characterizing reproductive toxicity after inhalation and oral exposure.

Developmental Toxicity. There are currently no data available in humans indicating that the inorganic tin and organotin compounds affect development after inhalation, oral, or dermal exposure. Likewise, there are no data in animals for the inorganic tin compounds and only oral data for the organotin compounds. Toxicokinetic data indicate that the inorganic tin compounds (Hiles 1974) do not transfer to the fetus. Bis(tributyltin)oxide was associated with decreases in fetal weights, skeletal abnormalities, and cleft palates in mice; maternal toxicity was also observed (Davis et al. 1987). These limited animal data suggest that birth defects will not be produced in humans at less than toxic doses for organotin compounds. However, like potential reproductive toxicity, further study of developmental outcomes in humans and animals after inhalation, oral, and dermal exposure would be useful in assessing potential risks of persons exposed in the vicinity of hazardous waste sites or occupational settings.

Immunotoxicity. There is currently no information available in humans or animals suggesting that the immune system may be one of the major targets of inorganic tin toxicity. Data are also lacking for the organatin compounds after inhalation, oral, and dermal exposures in humans and inhalation and dermal exposures in animals. However, studies of acute, intermediate, and chronic duration in rats and mice have suggested a specific action of the organotin compounds on the immune system of animals after oral exposure. Characteristic and consistent responses included atrophies of the thymus, spleen, lymph nodes, lymphocytopenia, delayed-type hypersensitivity reactions and decreases in serum immunoglobin concentrations (Funahashi et al. 1980; Krajnc et al. 1984; Seinen et al. 1977b; Smialowicz et al. 1989; Tennekes et al. 1989a, 1989b; Van Loveren et al. 1990). Data comparing the immunotoxic effects following exposure by the inhalation and dermal routes would be useful for evaluating the possibility that the effects are route- or species-specific. For humans exposed at hazardous waste sites or in the workplace, potential immunotoxic effects can be evaluated by performance of a battery of tests designed for this purpose. Immune system effects should be included in

any controlled prospective epidemiological studies in which exposure conditions are known.

Neurotoxicity. There are no studies in humans regarding neurotoxic effects after inhalation, oral, or dermal exposure to inorganic tin compounds. Animal data suggest that effects on the central nervous system have been associated with oral exposure to these compounds.

Neurotoxic effects have been reported for humans after inhalation exposure to organotin compounds and for humans and animals after oral exposure to these compounds. No effects were reported for the dermal routes of exposure. Symptoms preceding the death of the Stalinon patients included vertigo, headaches, photophobia, altered consciousness, visual impairment, convulsions, and sensory disturbances. Death was frequently from acute intracranial hypertension. Autopsies showed edema in the central nervous system white matter (Foncin and Gruner 1979). Studies of acute and intermediate-duration in animals demonstrated characteristic effects of the methyltin compounds. Tremors, hyperexcitability, aggressive behavior, and convulsions are often observed with the major histological change of neuronal alterations of the hippocampus (Brown et al. 1984; Chang et al. 1983). In addition, performance decrements in a series of behavioral toxicity tests have been reported (Reiter et al. 1980). Studies of developmental effects with special emphasis on neurotoxic effects would be useful in assessing a possible relationship for these end points. Considering the possibility of exposure at hazardous waste sites and in occupational settings, noninvasive neurobehavioral studies should be made of persons exposed to low levels of inorganic tin and particularly organotin compounds over various periods of time.

Epidemiological and Human Dosimetry Studies. The general population is exposed to inorganic tin compounds through consumption of contaminated food and drink, in industrial settings, and potentially at hazardous waste sites through contact with contaminated air, water, and soil. Organotin compounds are also used in agricultural and other uses which allow for potential exposure of people by different routes. Only limited case reports of human exposure and no retrospective or prospective epidemiological studies are available, Exposure concentrations of specific compounds are not quantified and the simultaneous exposure to multiple compounds makes interpretation of data difficult. Well-conducted and controlled epidemiological studies carried out near hazardous waste sites where tin exposures are likely or in occupational settings where tin compounds are used would contribute valuable data on possible adverse health effects in humans. Special emphasis should be placed on potential target organs and systems suggested from human and animal studies after different routes of administration. Included should be the incidence of pulmonary, liver, kidney, neurological, immunological, and reproductive effects.

Biomarkers of Exposure and Effect. Although tin and its compounds can be measured in tissues, blood, urine, and feces, it is difficult to quantitatively predict exposure levels from such determinations.

Knowing some potential target organs and systems affected by various tin compounds, it may be possible to develop biomarkers specific to effects. Examples include immunological and neurobehavioral tests as compound-specific pulmonary, liver, and kidney function studies. The primary objective of such biomarkers would be to predict adverse health effects in exposed individuals and populations.

Absorption, Distribution, Metabolism, and Excretion. Some animal studies of the absorption, distribution, and excretion of inorganic tin compounds after oral exposure have been reported. There are also data for the distribution of organotin compounds and excretion after exposures assumed to be oral but not always defined. Additional studies of inorganic tin compounds should focus on whether or not tin is excreted in the bile since this data is currently lacking. Information on the toxicokinetics of organotin compounds are needed in order to provide an understanding of their toxicity. Information is needed concerning the metabolism and fate of the tin and carbon moieties if the relative toxicities of these compounds are to be evaluated. Information on absorption, distribution, and excretion would also be helpful.

Comparative Toxicokinetics. Available toxicity data indicate some similar target organs for both inorganic and organic tin in both humans and animals. These include the brain, nervous system, liver, and kidney. However, no human or animal toxicokinetic studies are currently available to support similarities or differences in the kinetics of either inorganic tin or organotin compounds across species, including humans which help to elucidate the similarities in effects. It would, therefore, be useful to perform toxicokinetic studies in humans exposed particularly to organotin compounds at hazardous waste sites or in occupational or agricultural settings to better characterize any toxic effects observed. Detailed toxicokinetic studies related to suggested target organ toxicities would also be useful.

Mitigation of Effects. Recommended methods for the mitigation of effects of acute exposure to tin compounds include thorough washing or flushing with water for dermal/ocular exposure or administration of water to dilute ingested tin (Bronstein and Currance 1988). No information was located concerning mitigation of effects of lower-level or longer-term exposure to tin. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating tin-exposed populations in the vicinity of hazardous waste sites.

2.9.3 On-going Studies

A number of research projects are in progress investigating inorganic tin and organotin compounds. These projects are summarized in Table 2-9.

TABLE 2-9. On-going Studies on Tin and Compounds

Investigator	Affiliation	Research description	Sponsor
K. Anger	Oregon University of Health Sciences	Neurobehavioral assessment of workers in occupations or industries with chronic exposure to tin and other heavy metals with known neurotoxic properties.	NIOSH
H. L. Evans	New York University	Determine whether environmental toxicants such as the alkyltins can cause a decline in the capability for learning, memory, or vigilance in monkeys and the extent to which this decline resembles the decline associated with aging.	NIEHS
A. Kappas	Rockefeller University	Study the biological consequences of severe and sustained depletion of P-450 in liver and other tissues on metabolic endocrine homeostasis associated with organotins. Heme metabolism in the brain and gastrointestinal tract will be studied.	NIEHS

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
S. B. Sparber	Minnesota	Determine if undernutrition during the neonatal period, at a time several regions of the CNS of rats are still going through growth and proliferation, can render experimental subjects more vulnerable to neurotoxic effects later in life.	NICHHD
H. Tilson	NIEHS	Continuing study of triethyltin and trimethyltin neurotoxicity using a rat model.	NIEHS
J. H. Weber	University of New Hampshire	Study the accumulation and decomposition of tin compounds by bacteria that are resistant to its toxic effects on processes that involve tin compounds on algae, pore water/sediments, and shell-fish.	NSF
M. L. Woodruff	East Tennessee State University	Determine whether implantation of embryonic neural tissue is a biologically viable method of alleviating the consequences of toxic damage prolonged in the central nervous system by trimethyltin.	NIEHS

NICHHD = National Institute of Child Health and Human Development
NIEHS = National Institute of Environmental Health Sciences
NSF = National Science Foundation

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Table 3-l lists common synonyms, trade names, and other pertinent identification information for tin and representative inorganic tin and organotin compounds.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of tin and representative inorganic tin and organotin compounds.

TABLE 3-1. Chemical Identity of Tin and Compounds[a]

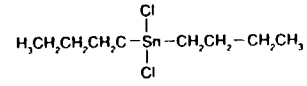
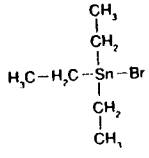
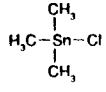
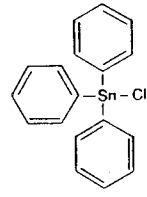
Characteristic	Tin	Stannous chloride	Stannic oxide	Dibutyltin chloride
Synonyms	Metallic tin; silver mat powder; tin flake	Tin salt; tin crystals; tin proto-chloride[b]	Stannic anhydride; tin peroxide; stannic acid[b]	Dibutyltin chloride dichlorodibutyltin; dichlorodibutyl-stannane
Trade name	No data	No data	No data	No data
Chemical formula	Sn	$SnCl_2$[c]	SnO_2[c]	$C_8H_{18}Cl_2Sn$
Chemical structure				
	Sn[d]	$SnCl_2$[d]	SnO_2[d]	
Identification numbers:				
CAS Registry	7440-31-5	7772-99-8[e]	18282-10-5[f]	683-18-1
NIOSH RTECS	XP7320000[g]	XP8700000[e]	XQ4000000[h]	WH7100000[e]
EPA Hazardous Waste	No data	No data	No data	No data
OHM/TADS	No data	7216909[h]	No data	No data
DOT/UN/NA/IMCO Shipping	No data	NA1759[h]	No data	No data
HSDB	5035[h]	0582[h]	5064[h]	6071[h]
NCI	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Tributyltin oxide	Triethyltin bromide	Trimethyltin chloride	Triphenyltin chloride
Synonyms	TBTO; bis(tributyltin) oxide; oxybis (tributyltin)	Stannane, bromomtriethyl-	Chlorotrimethyl stannane; chlorotrimethyltin; trimethyl chlorotin	Chlorotriphenyltin; triphenylchloro-stannane
Trade name	No data	No data	No data	No data
Chemical formula	$C_{24}H_{54}OSn_2$	$C_6H_{15}BrSn$	C_3H_9ClSn	$C_{18}H_{15}ClSn$
Chemical structure	$(H_3CCH_2CH_2CH_2)_3SnOSn(CH_2CH_2CH_2CH_3)_3$			
Identification numbers:				
CAS Registry	56-35-9	2767-54-6	1066-45-1	639-58-7
NIOSH RTECS	JN8750000[e]	WH6740000[e]	WH6850000[e]	WH6860000[e]
EPA Hazardous Waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO Shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	No data
NCI	No data	No data	No data	No data

[a]All information obtained from WHO 1980, except where noted.
[b]Windholz 1983
[c]Weast 1985
[d]Buckingham 1982
[e]Sax 1984
[f]Sax and Lewis 1987
[g]Sitting 1985
[h]HSDB 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Tin and Compounds[a]

Property	Information			
	Tin	Stannous chloride	Stannic oxide	Dibutylin dichloride
Molecular weight	118.69[c]	189.60[b]	150.69[b]	303.85
Color	White or gray[b]	White[b]	White[b]	White
Physical state	Solid[b]	Solid[b]	Solid[b]	Solid
Melting point	231.88°C[b]	246°C[b]	1,630°C[b]	43°C
Boiling point	2,260°C[b]	652°C[b]	1,800-1,900°C (subl.)[b]	135°C at 10 mmHg
Density at 20°C	7.28[b]	3.95[b]	6.95[b]	1.36
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble[b]	839,000 mg/L at 0°C[b]	Insoluble[b]	Soluble in hot water
Organic solvents	Soluble in hydrochloric and sulfuric acids[b]	Soluble in alcohol, ether, acetone[b]	No data	Soluble in ether, benzene, alcohol[d]
Partition coefficients:				
Log octanol/water	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor Pressure	No data	No data	No data	2 mmHg at 100°C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	335°F (168°C) (open cup)
Flammability limits	No data	No data	No data	No data
Conversion factors	Not applicable	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data	No data

TABLE 3-2 (Continued)

Property	Information			
	Tributyltin oxide	Triethlytin bromide	Trimethyltin chloride	Triphenyltin chloride
Molecular weight	596.16	285.81	199.26	385.47
Color	Colorless[c]	Colorless	No data	Colorless
Physical state	Liquid[c]	Liquid	Solid	Solid
Melting point	No data	-13.5°C	37°C	106°C
Boiling point	180°C at 2 mmHg[c]	224°C	No data	240°C at 13.5 mmHg
Density at 20°C	No data	1.630 g/mL	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Slightly soluble[c]	No data	No data	Insoluble
Organic solvents	Soluble[c]	Soluble	No data	Soluble
Partition coefficients:				
Log octanol/water	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor Pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	211°F (99°C) (closed cup)[e]	207°F (97°C) (closed cup)[e]	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not applicable	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data	No data

[a]All information obtained from Sax 1984, except where noted.
[b]Weast 1985
[c]Sax and Lewis 1987
[d]HSDB 1989
[e]Aldrich 1988

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The element tin comprises 0.0006% of the earth's crust (WHO 1980; Windholz 1983). Among the nine minerals containing tin are cassiterite (stannic oxide), stannate, and tealite (HSDB 1989). Of these, only cassiterite has commercial significance (WHO 1980). After tin-containing ores are mined, they undergo concentrating by either a gravity or magnetic separation process prior to smelting (HSDB 1989): Appreciable quantities of tin are obtained by recovery from tin-containing scrap materials (HSDB 1989; U.S. Bureau of Mines 1989; WHO 1980).

United States mine production of tin has been negligible between 1984 and 1988 (U.S. Bureau of Mines 1989). Currently, there is only a single tin-smelting facility in the United States which produces tin from tin ore (U.S. Bureau of Mines 1989). This facility, located in Texas City, Texas, produced approximately 3,500 metric tons of tin in 1988 from tin ore concentrates (domestic and imported) and recovered tin (U.S. Bureau of Mines 1989).

Twenty-five percent of the tin used in the United States is recovered from scrap materials containing tin. This secondary production occurs in the eastern parts of the United States at 7 detinning plants and 162 processing plants (U.S. Bureau of Mines 1989). The U.S. Bureau of Mines (1989) estimated that the 1989 consumption of primary tin in the United States will be 39,000 metric tons, most of which will be met by imports and the domestic recovery of tin from scrap materials.

4.2 IMPORT/EXPORT

Tin and tin ore quantities imported to the United States for consumption were 39,704 metric tons in 1986 (HSDB 1989), 44,103 in 1987 and estimated at 41,000 metric tons for 1988 (U.S. Bureau of Mines 1989).

No data were located regarding the import of tin compounds.

The United States export of tin ingots, pigs, and bars has varied between 1,300 and 1,550 metric tons per year between 1984 and 1988 (U.S. Bureau of Mines 1989).

No data were located regarding the export of tin compounds.

4.3 USE

The principal use of tin is in the making of containers (HSDB 1989), including aerosol cans and miscellaneous food and beverage containers (WHO 1980). Tin is also used as a reducing agent in chemical processes and in the production of other compounds such as stannous chloride, stannic oxide, and in the production of organotin compounds (HSDB 1989; WHO 1980). Tin is used to coat copper wire, and as a soldering material. Alloys of tin are used to make

dental materials (silver-tin-mercury) (WHO 1980), nuclear reactor components (tin-zirconium), aircraft components (tin-titanium) (WHO 1980), bronze (copper-tin), and brass (HSDB 1989). Tin is the principal component of pewter.

Inorganic tin compounds are used in the glass industry where they are used to give added strength to glass. Inorganic tin compounds also serve as the base for the formulation of colors, as catalysts, and in perfumes and soaps (WHO 1980).

Stannic oxide (cassiterite) is used as a polishing compound for both glass and metal. It is also used to produce milky or colored glass and is used in the formulation of fingernail polish (Windholz 1983).

Organotin compounds have various industrial uses. Disubstituted organotins are used in the production of plastics including food wrap where they act as stabilizers at 0.5%-2.0% by weight (WHO 1980). Disubstituted organotins are added to polyurethane foams and silicone to increase their strength and to minimize stickiness and odors (WHO 1980).

Trisubstituted organotins are useful biocides in agriculture and industry. They function as fungicides, bactericides, antihelminthics, and rodent repellents (WHO 1980). Tributyltins are used as antifoulants in marine paints but are restricted by the Organotin Antifouling Paints Control Act (June 16, 1988) which limits the type of vessel on which these paints can be used and sets acceptable release limits (U.S. Bureau of Mines 1989). Bis(tributyltin)oxide is used as a preservative for wood products, leather, ropes, fabrics, and paper.

4.4 DISPOSAL

Tin-containing wastes in the form of salts, slags, and muds are generated as a result of smelting, refining, and detinning processes (WHO 1980). Solid wastes containing tin are generated by both domestic and industrial users of containers (WHO 1980). Tin-containing wastes may be incinerated or disposed of in landfills (WHO 1980).

Tin is not listed as a hazardous waste constituent by the Environmental Protection Agency and therefore its disposal is not restricted by federal land disposal restrictions. No data were located regarding the amounts of tin disposed of by any means or trends in the disposal of tin.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Tin is a naturally-occurring element found in environmental media in inorganic and organic compounds. Tin may be released to the environment from natural and anthropogenic sources. The most significant releases of tin are from burning of fossil fuels and industrial production and use of tin. Tin compounds are generally only sparingly soluble in water and are likely to partition to soils and sediments. Photodegradation and biodegradation of organotins may occur at relatively slow rates. Organotin compounds may be significantly bioconcentrated by aquatic organisms.

Ambient environmental levels of tin are generally quite low, except in the vicinity of pollution sources. Humans may be exposed to tin by inhalation, ingestion, or dermal absorption. However, human exposure to tin is primarily by ingestion of food, especially canned food products.

Occupational exposure to tin may be significant in some industrial environments.

The EPA has identified 1,300 NPL sites. Tin has been found at 11 of the 1,177 evaluated sites. As more sites are evaluated by the EPA, the number may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-l.

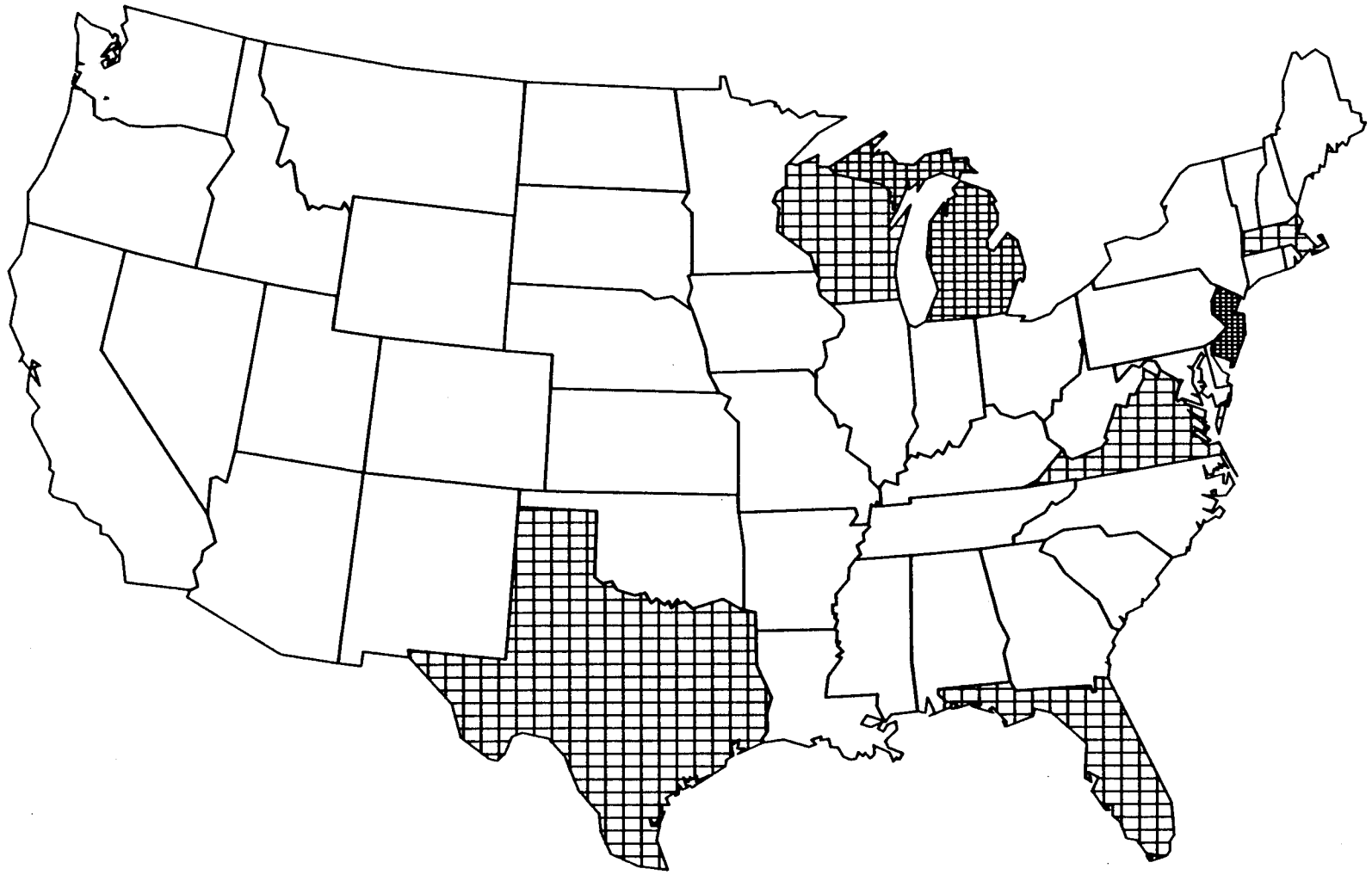
5.2 RELEASES TO THE ENVIRONMENT

Releases of tin to environmental media may occur from the production and use of tin and tin compounds. However, neither tin nor any tin compounds are listed on the SARA Section 313 toxic chemical list and, therefore, are not included in the Toxics Release Inventory (TRI).

5.2.1 Air

Tin may be released to the atmosphere from both natural and anthropogenic sources. Tin is a component of many soils and inorganic tin compounds may be released in dusts from wind storms, roads, and agricultural activities. Gases, dusts, and fumes containing tin may be released from smelting and refining processes, other industrial uses of tin and burning of fossil fuels (WHO 1980). Davison et al. (1974) reported the tin content of airborne fly ash from coal-burning power plants ranged from 7 to 19 μg/g. No other quantitative data on tin releases to air in the United States were located, but worldwide emissions of tin to the atmosphere from coal and oil combustion, refuse incineration, and copper/nickel production facilities were estimated at 1,470-10,810 metric tons in 1983 (Nriagu and Pacyna 1988).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH TIN CONTAMINATION *



* Derived from View 1989

5.2.2 Water

Releases of tin to water may occur from industrial facilities smelting, refining, or using tin (WHO 1980). Organotins may be released from agricultural uses or from their use as antifouling coatings on ships, and stabilizers in polyvinyl chloride plastic (EPA 1982a, 1988c; WHO 1980). No quantitative data were located regarding tin releases to water in the United States. However, the Organotin Antifouling Paints Control Act of 1988 restricts United States organotin paint usage on ships to those which do not exceed a release rate of 4 μg organotin/cm^2/day (EPA 1988c).

Elevated tin levels have been detected in both surface and groundwater at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate tin occurred at about 21% of the sites sampled at a geometric mean concentration of about 50 μg/L (CLPSD 1989). The CLP database includes data from both NPL and non-NPL sites. These values may be underestimates, since monitoring for tin was discontinued before 1986.

5.2.3 Soil

Tin may be released to soil from organotin pesticide usage and landfilling of tin-containing wastes, including used cans and organotin-containing plastics (WHO 1980).

More than 5,000 tons of organotins were released, primarily to landfills, in the United States in 1976 (Laughlin and Linden 1985). Additional releases to soil may occur by disposal of fly ash from coal combustion or land.application of sewage sludge.

Tin was detected in soil samples at 36% of 455 hazardous waste sites at a geometric mean concentration of 30 mg/kg (CLPSD 1989). The CLP database includes data from both NPL and non-NPL sites. These values may be underestimates, since monitoring for tin was discontinued before 1986.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Tin may be transported in the atmosphere by the release of particulate matter derived from the combustion of fossil fuels and solid wastes. The vapor pressure of elemental tin is negligible (Cooper and Stranks 1966). Tin in aerosol samples that existed in particulate-carbon masses was removed from the atmosphere predominantly by gravitational settling (Byrd and Andreae 1986). The half-life of airborne particles is usually on the order of days, depending on the size of the particle and atmospheric conditions (Nriagu 1979). Removal by washout mechanisms (such as rain) is thought to be unimportant.

However, there is little information on the potential for organotins to volatilize from water. There was no indication that tributyltin in water partitioned to the air during a 62-day period whereas 20% of the water evaporated (Maguire et al. 1983).

It has been speculated that the vapor pressures of some organotin compounds may be high enough such that they could partition to the atmosphere (Donard and Weber 1988; WHO 1980), but no actual measurements were available. The vapor pressure of one organotin, bis(tributyltin) oxide was estimated to be 8.4×10^{-10} atm and essentially nonvolatile (Maguire et al. 1983). Methyltins were not detected in rain-water samples (Byrd and Andreae 1986).

Tin in ambient waters may exist as divalent cationic (positively charged) ions (Sn^{2+}) or as quadrivalent ions (Sn^{4+}). Stannous tin (Sn^{2+}) dominates in reduced (oxygen-poor) water, and will readily precipitate as a sulfide (SnS) or as a hydroxide ($Sn(OH)_2$) in alkaline water. Stannic tin (Sn^{4+}) readily hydrolyzes, and can precipitate as a hydroxide (Wedepohl et al. 1978). The solubility product of $Sn(OH)_4$ has been measured as approximately 10^{-56} g/L at 25°C (Wedepohl et al. 1978).

The solubilities of organotin compounds in water are not well known. At ambient temperatures, their solubilities range from 10 μg/L to about 50 mg/L (Laughlin and Linden 1985; WHO 1980). It has been estimated that the solubility of bis(tributyltin) oxide ranges from 0.7 to 7 mg/L at pH 6 (Maguire et al. 1983).

Tin in water may partition to soils and sediments. Cations such as Sn^{2+} and Sn^{4+} will generally be adsorbed by soils to some extent, which reduces their mobility. Tin is generally regarded as being relatively immobile in the environment (WHO 1980). However, tin may be transported in water if it partitions to suspended sediments (Cooney 1988), but the significance of this mechanism has not been studied in detail.

The adsorption-desorption properties of inorganic tin have not been studied, and little information is available for organotins. Many organotins occur in water as cations, and would be expected to partition to soils and sediments. A partition coefficient of about 2,180 at 20°C was calculated by Maguire et al. (1985) to estimate the adsorption of tributyltin ions (as Bu_3Sn^+) by lake sediments. These investigations also concluded that the half-life of the desorption reaction was about 10 months, indicating that tributyltin can be strongly retained by sediments. Other studies (Cooney 1988; EPA 1988a; Strand 1983) have speculated that organotins may be bound by soil, but no additional information was located.

Tin may partition from water to aquatic organisms. An octanol/water partition coefficient (K_{ow}) describes the partitioning of an organic chemical between octanol and water. Octanol is believed to best imitate the fatty structures in plant and animal tissues (Kenaga and Goring 1980). The K_{ow} of tributyltin at pH 6 was reported as about 1,585 by Maguire et al. (1983). The most accurate K_{ow} for tributyltin in sea water was 5,500 (Laughlin and Linden

1985) and Tsuda et al. (1986) reported that the K_{ows} of seven organotin compounds ranged from 9 to 4,571. The magnitude of these values suggest that organotins can partition to fat tissues significantly, depending on the specific compound.

A bioconcentration factor (BCF) relates the concentration of a chemical in plants and animals to the concentration of the chemical in the medium in which they live. It was estimated that the BCFs of inorganic tin were 100, 1,000, and 3,000 for marine and freshwater plants, invertebrates, and fish, respectively (Thompson et al. 1972). Marine algae can bioconcentrate stannic tin by a factor of 1,900 (Seidel et al. 1980). No other experimentallyderived BCFs for inorganic tin were located. The BCF of tributyltin was estimated to be 473, but measured BCFs were always higher (Laughlin and Linden 1985). Bioconcentration factors for bis(tributyltin)oxide with marine oysters were measured as 2,300 to 11,400 (Waldock and Thain 1983). A BCF of 30,000 was estimated by Maguire et al. (1984) for the bioconcentration of tributyltin cation Bu_3Sn+ by freshwater green algae. Seven-day BCFs were derived for seven organotin compounds for muscle, liver, kidney, and vertebra tissue of carp (Tsuda et al. 1986). The BCFs ranged from 12 to 5,012; the highest factors were found for tributyltins. However, these factors were not based on steady-state conditions, and may be low estimates. No information was located on the food chain and biomagnification of inorganic or organic tin.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No information was located on the transformation or degradation of tin compounds in the atmosphere.

5.3.2.2 Water

There is no evidence that the valence of inorganic tin is influenced directly by microbial processes (Cooney 1988). It has been established that inorganic tin can be transformed into organometallic forms by microbial methylation (Hallas et al. 1982). Inorganic tin may also be converted to stannane (H_4Sn) in extremely anaerobic (oxygen-poor) conditions by macroalgae (Donard and Weber 1988).

It has been reported that low concentrations of tributyltin fluoride were readily transformed to tributyltin chloride in sea water (Strand 1983). Tributyltin has been shown to undergo slow photolysis (Maguire et al. 1983). The half-life of the photolysis reaction was estimated to be greater than 89 days. The direct photolysis of tributyltin in water initiates a sequential removal of the butyl groups, leading to inorganic tin as a residual. The reaction was much faster in the presence of fulvic acid (a major component of soil organic matter).

The biodegradation of organotins in water may or may not be a slow process. Under laboratory conditions, Maguire and Tkacz (1985) estimated that the half-life of tributyltin in water was about 35 weeks in the dark, and like photolytic reactions, involved debutylation. They concluded that tributyltin was a fairly persistent chemical in the environment. The overall half-life of tributyltin (photolysis and biodegradation) in water was estimated to be on the order of months in Canadian lakes. However, the half-life of tributyltin in river waters in Georgia was estimated to be between 3 and 13 days (Lee et al. 1989). The degradation of the chemical was attributed to microalgae whereas direct photolysis did not appear to be important. The half-life of tributyltin via degradation by algae in water/sediment mixtures was estimated to be about 25 days (Maguire et al. 1984), but the concentration of algae used in the experiment was much greater than that expected in lakes (Maguire and Tkacz 1985).

5.3.2.3 Soil

Organotins may also be slowly biodegraded when in contact with soils and sediments. Alkane-utilizing bacteria were isolated from soil that could degrade the tributyl forms to di- and monobutyltin, but further breakdown was not observed.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Tin is detected in air infrequently at low concentrations, except in the vicinity of industrial sources. Air concentrations in United States cities ranged from below the detection limit to 0.8 $\mu g/m^3$ in several studies (WHO 1980). Average concentrations are generally <0.1 $\mu g/m^3$, with the higher concentrations near some industrial facilities (EPA 1982a; WHO 1980). In some studies, tin was not detected in 40% to more than 50% of samples (WHO 1980). Atmospheric tin is associated with particulate matter and peak concentrations were found on smaller respirable particles (1 to 3 μm) (WHO 1980).

5.4.2 Water

Tin occurs in trace amounts in natural waters. However, it is seldom measured and only infrequently detected, since concentrations are often below the detection limit (NAS 1977; WHO 1980). In surface waters, tin was detected in only three of 59 samples from 15 United States and Canadian rivers at concentrations ranging from 1.3 to 2.1 $\mu g/L$, and not detected in 119 samples from 28 United States rivers. A mean tin concentration of 0.038 $\mu g/L$ was reported for surface water in Maine (NAS 1977; WHO 1980). Organotin concentrations in the Detroit and St. Clair Rivers ranged from not detected to 0.11 $\mu g/L$ (Maguire et al. 1985).

Tin concentrations in public water supplies reportedly ranged from 1.1 to 2.2μg/L in 42 United States cities and from 0.8 to 30 μg/L in 32 of 175 water supplies in Arizona (NAS 1977; WHO 1980). Tin is present in seawater at about 0.2-3 μg/L (NAS 1977; WHO 1980).

Tributyltin has been monitored in harbor areas due to concern about release of this compound to water from antifouling paints and its toxicity to aquatic life. Concentrations reported ranged from not detected to 0.8 μg/L (EPA 1988c). Reported total organotin concentrations in surface water ranged from 0 to 900 mg/L (EPA 1982a).

5.4.3 Soil

Tin concentrations have been reported in sewage sludge from 23 United States cities ranging from 11 to 1,300 mg/kg (Mumma et al. 1984). Organotin concentrations in sediments from the Detroit and St. Clair Rivers ranged from not detected to 0.036 mg/kg (Maguire et al. 1985).

Soil concentrations of tin generally range up to 200 mg/kg, but in areas of high tin deposits levels of 1,000 mg/kg may occur (Schafer and Fembert 1984; WHO 1980). Mean background soil concentration in the U.S. is 0.89 mg tin/kg (Eckel and Langley 1988).

5.4.4 Other Environmental Media

Most natural foods contain small amounts of tin but canned foods may have significant tin levels (NAS 1977; WHO 1980). Tin concentrations in fresh meats, cereals, and vegetables reportedly range from 0.1 to 1.0 mg tin/kg (Schafer and Femfert 1984). However, concentrations of tin ranging from 1.8 to 500 mg/kg have been reported in canned foods (Schafer and Femfert 1984; Sherlock 1987), with usual values below 100 mg/kg (NAS 1977). Foods from all-lacquered cans usually had tin concentrations below 25 mg/kg (WHO 1980). Current data from the Can Manufacturers Institute (CM1 1988) indicate that more than 90% of tin-lined cans used for food today are lacquered. Only light colored fruit and fruit juices are packed in unlacquered cans, since tin helps maintain the color of the fruit.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to tin may occur by inhalation, ingestion, or dermal contact. However, exposure of the general population occurs primarily by ingestion of food (NAS 1977; WHO 1980). Estimates of daily dietary tin intake range from 1 mg for diets consisting mainly of fresh meats, vegetables, and cereals, to 38 mg from diets including a high proportion of canned foods (Schafer and Femfert 1984; WHO 1980). The average daily tin intake of an adult in the United States was estimated at 4.003 mg; 4 mg from food, 0.003 mg from air, and with undetectable levels contributed by drinking water (EPA 1987a; WHO 1980). Other estimates of human daily intake range from 0.2 to 17 mg (Klaassen et al. 1986; Krigman and Silverman 1984). Tin was detected in

human adipose tissue samples during the 1982 National Human Adipose Tissue Survey at concentrations ranging from 8.7 to 15 μg/g (Stanley 1986).

Occupational exposures to tin may be substantial. Inhalation or dermal exposure to triphenyltin leachate, used in fungicides and insecticides, may occur during both manufacturing and application (NAS 1977; WHO 1980). Workers in the numerous industries producing or using inorganic tin or organotin compounds (Section 4.3) may also be exposed. The National Institute for Occupational Safety and Health estimated that 730,000 workers in the United States were potentially exposed to tin in the workplace in 1980 (NOES 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure to workers to tin or any of its compounds. These surveys provide only estimates of number of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Potentially high inhalation exposures to tin and its compounds may occur in the workplace or in agricultural uses of tin compounds.

Individuals who eat canned foods as a major portion of their diets or who store food, especially acidic foods, in opened cans may have potentially above-average exposure to inorganic tin by ingestion. In addition, those populations living near hazardous waste sites where high levels of tin have been detected may be exposed to higher than background levels of tin.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of inorganic tin or organotin compounds is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of inorganic tin or organotin compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The chemical behavior of most of the common organotin compounds in environmentally-relevant media are not well known. There is a need to measure the solubility and vapor pressure of the more important organotin compounds in order to provide a more reliable basis for predicting their fate in the environment.

Production, Import/Export, Use, and Disposal. Production volumes and uses of tin and tin compounds are well-documented (HSDB 1989; U.S. Bureau of Mines 1989; WHO 1980). However, data on releases, disposal practices, and possible environmental contamination from uses of tin and its compounds are limited. Since tin is not on the TRI and is not listed as an EPA hazardous waste constituent, current data are not available on industrial releases or disposal practices. Information on releases or disposal practices, and current quantitative data on leaching of inorganic and organic forms of tin into foods from tin-lined cans and polyvinyl chloride packaging materials would be useful in assessing potential human exposure to tin compounds.

Environmental Fate. Few data are available on the partitioning, transport, or transformation of tin compounds. From the information available it appears likely that both inorganic and organotin will partition to soils and sediments, but will not volatilize from water (Cooney 1988; Maguire et al. 1983, 1985; WHO 1980). Little is known about the degradation or transformation of tin compounds in air, water, or soil. The information that is available is at best semi-quantitative and geographically-specific (Lee et al. 1989; Maguire et al. 1983, 1984; Maguire and Tkacz 1985). Research on physical and biological processes in water and at sediment-water interfaces would be particularly helpful to more accurately predict the fate of tin compounds released to the environment.

Bioavailability from Environmental Media. Inorganic tin is not well absorbed after inhalation, oral, and dermal exposure. Organotins are somewhat better absorbed by both the inhalation and oral routes, but dermal absorption is not considered important (Hiles 1974; Mori et al. 1984). The daily intakes of tin from air, food, and water are small (WHO 1980). Studies on the availability of tin compounds from soils would be useful in assessing human exposure from ingesting contaminated soils. Further study of human intake of organotin compounds from food and water would also be useful.

Food Chain Bioaccumulation. It has been established that organotins can be bioconcentrated by aquatic organisms in marine environments (Laughlin and Linden 1985; Waldock and Thain 1983). Similar information for terrestrial ecosystems would be useful. Inorganic tin compounds may also be bioconcentrated but data are limited (Seidel et al. 1980; Thompson et al. 1972). There is no information available on the potential transfer of inorganic tin or organotin compounds from lower trophic levels to higher levels. This information would be useful because studies have shown that organotin can be bioconcentrated significantly. However, bioconcentration properties of individual organotin compounds would vary.

Exposure Levels in Environmental Media. Current data on tin levels in air, water, and food are limited (EPA 1982a, 1988c; NAS 1977; WHO 1980). Additional information on inorganic and organotin concentrations in all media, especially air, water, and soil at hazardous waste sites, determined by the most sensitive analytical methods, would be useful in evaluating human exposure to tin.

Several estimates concerning the human daily intake of tin have been reported (EPA 1987; Klaassen et al. 1986; Krigman and Silverman 1984; WHO 1980). However, these estimates are not based on recent monitoring data and need to be revised in accordance with current data. Since canned food is a primary source of tin exposure, data on current levels of tin in canned foods and revised estimates of daily intake would help to better evaluate human exposure to tin.

Exposure Levels in Humans. Tin has been detected in human adipose tissue (Stanley 1986), but the data are not current. No data were available on biological monitoring for tin in other tissues. Biological monitoring data, especially for populations near hazardous waste sites, would help to assess human exposure to tin.

Exposure Registries. No exposure registries for tin were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No on-going studies on the fate, transport, or exposure potential of tin were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring tin in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify tin. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect tin in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Tin is usually determined as the total metal, but it may also be measured as specific organotin compounds. Flame atomic absorption analysis is the most widely used and straightforward method for determining tin; furnace atomic absorption analysis is used for very low analyte levels and inductively coupled plasma atomic emission analysis is used for multianalyte analyses that include tin.

6.1 BIOLOGICAL MATERIALS

Methods for the determination of tin in biological materials are summarized in Table 6-1.

Normally, for determination in biological samples, the sample is digested in an oxidizing acid mixture followed by atomic spectrometric determination. Organotin can be extracted from biological samples and determined by atomic spectrometric methods or gas chromatography, usually after derivatization.

6.2 ENVIRONMENTAL SAMPLES

Methods for determination of tin in environmental samples are summarized in Table 6-2.

Tin is readily measured in multielement analyses of air, water, and solid waste samples by inductively coupled plasma atomic emission spectroscopy. For individual analyses of tin, direct aspiration atomic absorption spectroscopy is usually used. Organotin can be extracted from environmental samples and determined by atomic spectrometric methods or gas chromatography, usually after derivatization.

TABLE 6-1. Analytical Methods for Determining Inorganic Tin and Organotin Compounds in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Total inorganic tin					
Biological material[a]	Digestion of biological materials	Atomic spectrometric	No data	No data	Angerer and Schaller 1988
Urine	Digest in oxidizing acid, extract ketone as the cupferon chelate	Colorimetry	<50 µg/L[b]	98%-106%	Baselt 1988
Urine	Extraction with poly-dithiocarbamate resin, which is ashed	ICP/AES	2 µg/L	100±10% recovery	Kneip and Crable 1988
Urine	Extract with resin, ash resin	ICP/AES	0.1 µg	100±10%	NIOSH 1984a
Food	Digest in oxidizing acid	AAS	No data	No data	AOAC 1984b
Organotins and metabolites					
Fruit	No data	Spectro-photometry (dithiol method)	0.2 µg	~98%	Corbin 1970
Biological materials, tissue	Homogenized, hydrochloric acid added, extracted with ethyl acetate	HPLC/fluor-escence[c]	0.1-1 ng	91%-100%	Yu and Arakawa 1983
Biological materials	Elution stepwise on silica gel column	AAS	1.5 ng	72.7±9.3%	Iwai et al. 1981

[a]A digestion procedure for metals in biological materials applicable to most metals, including tin.
[b]Estimated from sensitivity and linearity data.
[c]Fluorescence detection after derivitization with Morin reagent

AAS = atomic absorption spectroscopy; HPLC = high performance liquid chromatography; ICP/AES = inductively coupled plasma atomic emission spectroscopy

TABLE 6-2. Analytical Methods for Determining Inorganic Tin and Organotin Compounds in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Total inorganic tin					
Environmental	Digested in oxidizing acid	ICP/MS	0.04-50 ng/g	103±3%	Brzezinska-Paudyn and Van Loon 1988
Water	Generate hydride with sodium borohydride or electrolytically, sweep into silica cell heated to 700°C	AAS	0.02 µg/L	No data	Rains 1982
Water (aqueous solution)	Generate hydride with sodium borohydride or electrolytically, sweep into silica cell heated to 700°C	AAS	0.5 µg/L	No data	Thompson and Thomerson 1974
Water	Acidify with nitric acid	AAS (direct aspiration)	0.8 mg/L	No data	APHA 1989c
Water	Acidify with nitric acid	AAS (furnace technique)	5 µg/L	No data	APHA 1989a
Water[a]	Acidify with nitric acid	ICP/AES	No data	No data	APHA 1989d
Water	Acidify with nitric acid	AAS (direct aspiration)	0.8 mg/L	No data	EPA 1983a
Water	Acidify with nitric acid	AAS (furnace technique)	5 µg/L	No data	EPA 1983b
Sediments, sludges, soils	Acid digestion procedure for subsequent atomic spectrometric analysis	AAS, ICP/AES	Not applicable	Not applicable	EPA 1986a
Waste effluent, solid wastes	Acidify with nitric acid, digest if necessary	AAS (direct aspiration)	0.8 mg/L in water	96±6% at 4 mg/L	EPA 1986b
Pesticide formulations	Form volatile organotin derivatives	GC/FID	No data	No data	Basters et al. 1978
Organotins					
Pesticide	Derivatize, extract with toluene	GC/FID	No data	No data	AOAC 1984a

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Organotins (Cont.)					
Air	Adsorbed onto Chromosorb 102 desorption with ethereal hydrochloric acid, methylated	GC/FID	0.05 µg/m^3	93.3±9.3%	Zimmerli and Zimmerman 1980
Air	Adsorption on filter and XAD-2 resin, desorption	AAS (furnace technique)	1 µg	No data	NIOSH 1984b
Water	Acidified, extracted with tropoloin benzene, derivatized	GC/FPD	100 pg	96±4% to 103±8%	Maguire and Huneault 1981
Water	Generate hydrides with sodium borohydride, separate hydrides by boiling point	AAS	2 ng	No data	Hodge et al. 1979
Water	Generate hydride derivatives	AAS	<0.1 µg/L tributyltin	No data	Lee et al. 1989
Water	Extract in n-hexane, produce fluorescent morin derivative	Fluorescence	0.001-0.5 nmol/mL	91.3±0.6 to 99.7±0.5% recovery	Arakawa et al. 1983

[a]Tin not listed specifically as an analyte, but can be determined by ICP/AES

AAS = atomic absorption spectrometry; GC/FID = gas chromatography/flame ignition detector; GC/FPD = gas chromatography/flame photometric detector; ICP/AES = inductively coupled plasma atomic emission spectroscopy; ICP/MS = inductively coupled plasma with mass spectrometric detection

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tin is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tin.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive and selective methods are available for the detection and quantitative measurement of tin after the sample matrix in which it is contained has been properly treated. Atomic spectrometric techniques provide methods for the determination of tin that have low detection limits, are highly specific, and are readily available (Angerer and Schaller 1988; AOAC 1984b; Kneip and Crable 1988; NIOSH 1984a). Methods for the determination of specific compounds that contain tin are more difficult and less well developed than are methods for the determination of total tin, but this is an important concern because of the widespread use of organotin compounds as preservatives in industry and in other applications.

No methods have been identified that can be used to associate the level and extent of exposure to tin and specific tin compounds with levels of tin in biological materials such as human tissues or fluids. It would be useful to have such methods to make these correlations.

Similarly, no methods have been identified that can be used to directly associate levels of tin and specific tin compounds in biological samples with the onset of adverse health effects. If such methods were available, it would be possible to correlate the level or severity of effects with the level and extent of exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining tin in water, air, and waste samples with excellent selectivity and sensitivity are well developed and undergoing constant improvement.

Sampling methodologies for very low level elemental pollutants such as tin continue to pose problems, including nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction, and purification procedures (Green and LePape 1987).

6.3.2 On-going Studies

Examination of the literature suggests that studies are underway to improve means for determining tin and other heavy metals in biological samples and environmental media. Improvements continue to be made in detection limits and ease and speed of analysis.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for tin by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Tin and Compounds

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA		OSHA 1989
	Inorganic compounds, except oxides, as Sn	2 mg/m^3	(29 CFR 1910.1000)
	Organic compunds, as Sn	0.1 mg/m^3 skin	Table Z-1-A
	Tin oxide, as Sn	2 mg/m^3	
b. Water:			
EPA OWRS	General permits under NPDES	Yes	40 CFR 122,
	Total tin		Appendix D,
			Table IV
U.S. Congress	Organotin Antifouling Paint Control Act of 1988	4 μg organotin/ cm^2/day	EPA 1988c (Pub. Law 100-333)
c. Food:			
FDA	Indirect food additives	Yes	FDA 1989
	Adhesives and components of coatings and polymers		(21 CFR 155.200, 172.810,
	Dibutyltin oxide, hydroxybutyltin monobutyltin		175.300, oxide, 177.2420,
	tris(2-ethylhexoate, stannous chloride)		184.1845)
d. Other:			
EPA OPP	Cancellation/Restriction of Registration for Tributyltin Antifoulants	Yes	EPA 1988c
EPA OSW	Groundwater monitoring list (Appendix IX) (Total tin)	Yes	EPA 1987c (40 CFR 261)
EPA OTS	Health and Safety Reporting Rule	Yes	EPA 1988d
	Dibutyltin dilaurate		(40 CFR 716.120)
	Dibutyltin bis(lauryl mercaptide)		
	Dibutyltin bis(isooctylmaleate)		
	Monobutylin tris(isooctyl) mercaptoacetate		
	Preliminary Assessment Information Reporting Rule	Yes	40 CFR 712.30
	Dibutyltin dilaurate		
	Dibutyltin bis(lauryl mercaptide)		
	Dibutyltin bis(isooctylmaleate)		
	Monobutylin tris(isooctyl) mercaptoacetate		
	Dimethyltin S,S' bis(isooctyl mercaptoacetate)		
	Dibutyltin S,S' bis(isooctyl mercaptoacetate)		
	Monomethyltin tris(isooctyl mercaptoacetate)		

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
Guidelines:			
a. Air:			
ACGIH	TLV TWA		ACGIH 1990
	Metal	2 mg/m³	
	Oxide and inorganic compounds, except SnH_4, as Sn	2 mg/m³	
	Organic compounds, as Sn	0.1 mg/m³ skin	
NIOSH	REL TWA	2 mg/m³	NIOSH 1990
b. Other:			
EPA	Carcinogenic Classification		EPA 1987
	Tin and Compounds		
	RfD (oral)	0.6 mg/kg/day[a]	
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations, as Sn		NATICH 1989
Connecticut		40 µg/m³ (8 hr)	
Nevada		4.80E-2 mg/m³ (8 hr)	
North Dakota		2.0E-2 mg/m³ (8 hr)	
Virginia		1.60 µg/m³ (24 hr)	

[a] This value is undergoing Agency review, but has not been validated (EPA 1992).

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; Sn = tin; TLV = Threshold Limit Value; TWA = Time-Weighted Average; U.S. = United States

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism..

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration($_{Lo}$) (LC_{Lo}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration($_{50}$) (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Doset($_{Lo}$) (LD_{Lo}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose($_{50}$) (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time($_{50}$) (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency

or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q,* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m3 for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

9. GLOSSARY

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10) Reference The complete reference citation is given in Chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm. See LSE Figure 2-l

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13) Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation-exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Unner-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (cl,*).

(19). Kev to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

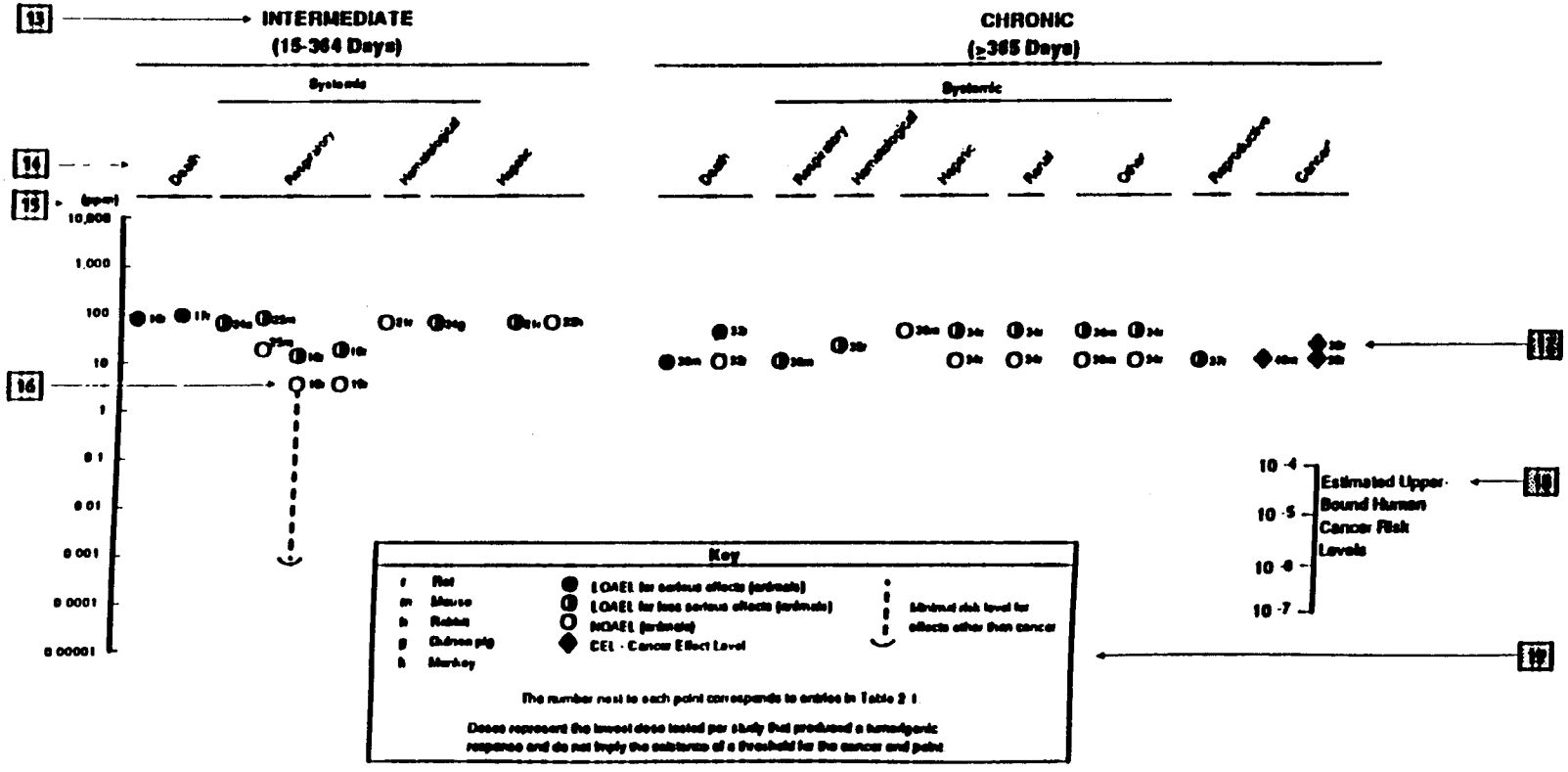

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. #Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information frommultiple species is available) with the highest NOAELthat does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and
CFR	Liability Act
CLP	Code of Federal Regulations
cm	Contract Laboratory Program
CNS	centimeter
DHEW	central nervous system
DHHS	Department of Health, Education, and Welfare
DOL	Department of Health and Human Services
ECG	Department of Labor
EEG	electrocardiogram
EPA	electroencephalogram
EKG	Environmental Protection Agency
FAO	see ECG
FEMA	Food and Agricultural Organization of the United Nations
FIFRA	Federal Emergency Management Agency
f_1	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	first generation
ft	feet per minute
FR	foot
g	Federal Register
GC	gram
HPLC	gas chromatography
hr	high performance liquid chromatography
IDLH	hour
IARC	Immediately Dangerous to Life and Health
IL0	International Agency for Research on Cancer
in	International Labor Organization
Kd	inch
kg	adsorption ratio
Koc	kilogram
Kow	octanol-soil partition coefficient
L	octanol-water partition coefficient
LC	liter
LC_{Lo}	liquid chromatography
LC_{50}	lethal concentration low
LD_{Lo}	lethal concentration 50 percent kill
LD_{50}	lethal dose low
LOAEL	lethal dose 50 percent kill
LSE	lowest-observed-adverse-effect level
m	Levels of Significant Exposure
	meter

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mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppc f	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
run	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to

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=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for tin. The panel consisted of the following members: Dr. Hugh L. Evans, Director, Laboratory for Behavioral Toxicology, Institute of Environmental Medicine, New York University Medical Center; Dr. Joseph P. Gould, Research Scientist, School of Civil Engineering, Georgia Institute of Technology; and Dr. Elizabeth T. Snow, Assistant Professor, Institute of Environmental Medicine, New York University Medical Center. These experts collectively have knowledge of tin's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.